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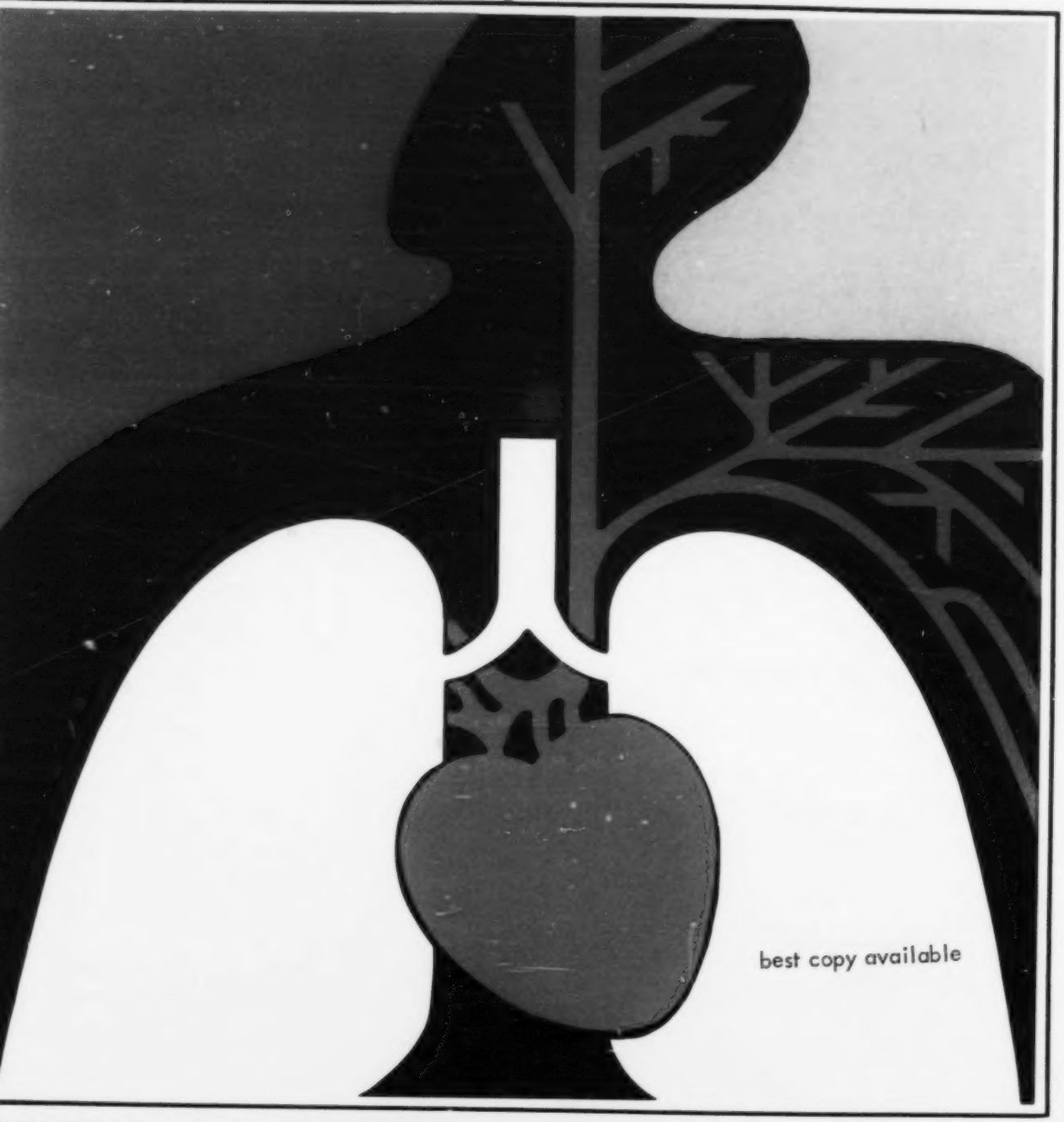
Volume 1

Report of the Working Group on Arteriosclerosis of the National Heart, Lung, and Blood Institute

Summary, Conclusions, and Recommendations



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Volume 1

Report of the Working Group on Arteriosclerosis of the National Heart, Lung, and Blood Institute

Summary, Conclusions, and Recommendations

Prepared by the Working Group on Arteriosclerosis
of the National Heart, Lung, and Blood Institute
National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Members of the Working Group on Arteriosclerosis

Chairman
Alfred P. Fishman, M.D.
William Maul Measey Professor of Medicine
Director, Cardiovascular-Pulmonary Division
Department of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Sidney Blumenthal, M.D.
Vice President
American Bureau for Medical Advancement in China
New York, New York

Lawrence S. Cohen, M.D.
Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

M. Bernadette Garvey, M.D.
Associate Professor
Department of Medicine
University of Toronto
Toronto, Ontario, Canada

Edgar Haber, M.D.
Professor of Medicine
Harvard Medical School
Chief, Cardiac Unit
Massachusetts General Hospital
Boston, Massachusetts

David A. Hamburg, M.D.
Director, Division of Health Policy Research and Education
John F. Kennedy School of Government
Harvard University
Cambridge, Massachusetts

Henry C. McGill, Jr., M.D.
Professor, Department of Pathology
University of Texas Health Science Center
Scientific Director
Southwest Foundation for Research and Education
San Antonio, Texas

Alex V. Nichols, Ph.D.
Professor of Biophysics and Medical Physics
Department of Biophysics and Medical Physics
University of California
Berkeley, California

M. Jeanne Pontious, R.N.
Associate Professor of Nursing
School of Nursing
Indiana University
Indianapolis, Indiana

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John Ross, Jr., M.D.
Professor of Medicine
Head, Division of Cardiology
University of California at San Diego School of Medicine
La Jolla, California

Russell Ross, Ph.D.
Professor of Pathology and Biochemistry
University of Washington School of Medicine
Seattle, Washington

David C. Sabiston, Jr., M.D.
James B. Duke Professor and Chairman
Department of Surgery
Duke University Medical Center
Durham, North Carolina

Reuel A. Stallones, M.D., M.P.H.
Dean, School of Public Health
University of Texas
Houston, Texas

Jeremiah Stamler, M.D.
Professor and Chairman
Department of Community Health and Preventive Medicine
Dingman Professor of Cardiology
Northwestern University Medical School
Chicago, Illinois

James F. Toole, M.D.
Walter F. Teagle Professor of Neurology
Chairman
Department of Neurology
Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, North Carolina

Donald B. Zilversmit, Ph.D.
Professor of Nutritional Biochemistry
Division of Nutritional Sciences
Cornell University
Ithaca, New York

Institute Staff

John B. Dunbar, D.M.D., Dr. P.H.
Special Assistant
Office of the Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Jay Moskowitz, Ph.D.
Associate Director for Program Planning and Evaluation
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

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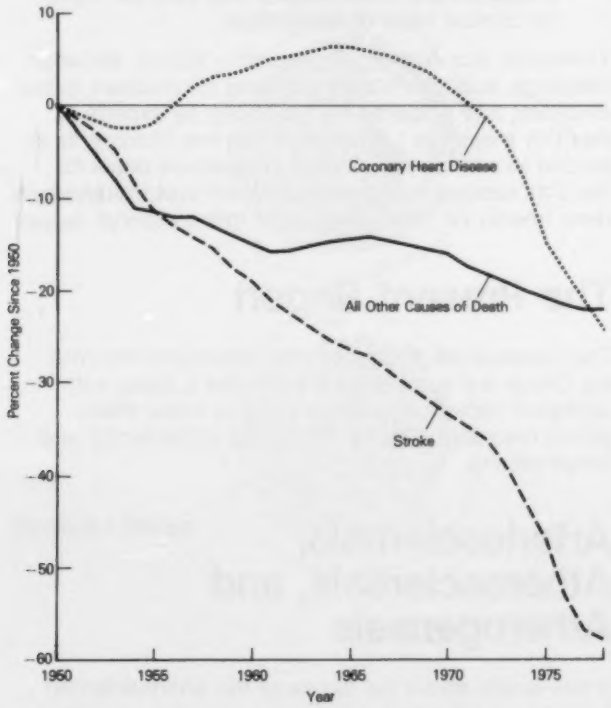
Introduction

Arteriosclerosis exacts a devastating national and personal toll not only on life expectancy but on the quality of life. The arteriosclerotic diseases, particularly coronary heart disease and cerebrovascular disease (stroke), cause more deaths, disability, and economic loss in the United States than any other group of acute or chronic diseases. In 1977, arteriosclerosis caused 873,000 deaths—almost half of all deaths in the United States. In that year, arteriosclerosis cost an estimated $39 billion in health expenditures and lost productivity. Among all chronic diseases, arteriosclerosis is the leading cause of days lost from work, i.e., days spent at home, in hospitals, or in nursing homes.

Because of the magnitude of this health problem, 10 years ago the National Heart and Lung Institute sponsored a Task Force on Arteriosclerosis. The report of this group in 1971 summarized the understanding of the disease at that time and identified areas of research, development, and applications to health care that should be explored.



*Age-Averaged.

Figure 1.
Percent Change in Death Rates* Since 1950 for Coronary Heart Disease, Stroke, and All Other Causes, Ages 35-74, United States, 1950-1978

During the ensuing decade, almost all of the Task Force recommendations were implemented by the National Heart, Lung, and Blood Institute (NHLBI). These were years of extraordinary progress as exemplified by three areas of accomplishment:

1. advances in fundamental research on the causes and mechanisms of arteriosclerosis and its complications: coronary heart disease, stroke, and peripheral vascular disease;
2. progress with clinical trials to evaluate new knowledge with respect to the prevention, control, and treatment of these diseases; and
3. incorporation of new knowledge of the arteriosclerotic diseases into the general armamentarium of clinical medicine and public health, thereby improving prevention and treatment.

Decline in Mortality

These achievements confirmed that progress is possible, both in research to understand the arteriosclerotic diseases, and in application to control them. The decline in mortality from coronary heart disease illustrates this point. Premature death from coronary heart disease had increased year after year through the decades of the 1940's and 1950's, to become the major health problem of adults—particularly men—in the United States. Therefore, reversal of this trend in the mid-1960's followed by a sustained and progressively steeper decline in the 1970's is an event of great scientific importance and sweeping social consequence (Figures 1, 2). Mortality rates from coronary heart disease have decreased more than 25 percent in 10 years.

Mortality from stroke also declined. However, the pattern differs from that of coronary heart disease: for stroke the decline began earlier in the century; during the past decade the decline has occurred at a markedly accelerated rate. The percent decrease in mortality from 1968 to 1978 was even greater than the percent decrease in coronary heart disease (Figure 2).

As a consequence of the decline in death rates from the two main forms of adult cardiovascular disease—coronary heart disease and stroke—mortality from all cardiovascular diseases fell markedly, by almost 30 percent for the 35-74 age group. In that age group more than 800,000 deaths from cardiovascular diseases were prevented in the decade from 1969 through 1978; of these, 165,000 (20 percent) were prevented in 1978 alone.

Not all industrialized countries experienced the same pattern of change in mortality from coronary heart disease as did the United States. In a few, such as Australia and Canada, the decreases were appreciable, but less than in the United States. In contrast, in many countries, such as Hungary, Ireland, New Zealand, and Sweden, the mortality rates increased (Table 1).

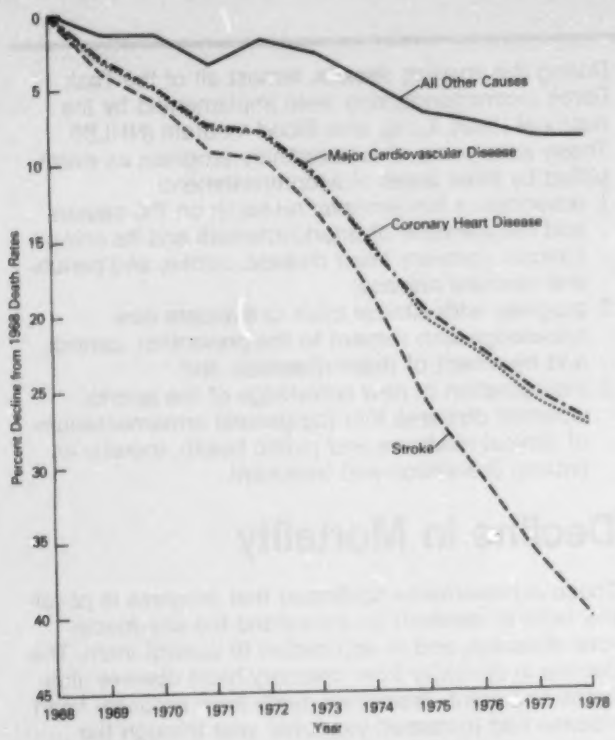


Figure 2.
Trends in Cardiovascular Disease and All Other Causes of Mortality: Decline by Age-Adjusted Death Rates, Ages 35-74, 1968-1978, United States

At the same time, these gains underscored unfinished tasks that lie ahead, for, despite the declines in mortality, the Nation continues to be heavily burdened (more so than most other countries in the world) by premature sickness, disability, death, economic loss, and human misery from the atherosclerotic diseases, particularly coronary heart disease (Appendix A) (Tables 1, 2, 3).

Charge to the Working Group

Stimulated on the one hand by accomplishments and on the other by still unmet needs, the Director of the National Heart, Lung, and Blood Institute, Dr. Robert I. Levy, judged the time to be appropriate for a fresh assessment of arteriosclerosis, with particular reference to opportunities in research and application. Before initiating this appraisal, in 1978 he commissioned a review group to assess the impact of the 1971 Report by the NHLI Task Force on Arteriosclerosis. This review group concluded that the contents and recommendations of the 1971 Report had been valuable both to the NHLBI and to scientists in identifying fruitful lines of research and application. It recommended that a second appraisal be carried out expeditiously, using a similar approach. The NHLBI Director appointed a Working Group, similar to the original Task Force, to conduct the appraisal. The members of the Working Group are listed at the beginning of this volume.

At its initial meeting on October 8, 1978, the Working Group received the following instructions from the Director of the National Heart, Lung, and Blood Institute:

1. The Working Group has been constituted to undertake a broad assessment of arteriosclerosis, from its basic processes to the prevention, diagnosis, treatment, and rehabilitation of persons suffering from its clinical sequelae.
2. The Institute's responsibility has been extended from basic research and clinical trials to include the translation and application of research findings through demonstration and education programs.
3. For each element of this broad field, the Working Group is asked to:
   a. assess present understanding;
   b. highlight unresolved problems; and
   c. emphasize opportunities for research, with particular attention to preventive measures, therapies, and technologies that may be ready for clinical trials or application.

Thereafter, the Working Group met monthly. Between meetings, subcommittees gathered information, sifted evidence, and prepared for testimony by experts at monthly meetings.* A separate volume (Volume II), intended to provide an in-depth substantive basis for the conclusions and recommendations of Volume I, drew heavily on the testimony of these experts.

The Present Report

The conclusions and recommendations of the Working Group are summarized in Volume I, along with sufficient background information to make these points meaningful to the interested nonscientist and nonphysician.

Arteriosclerosis, Atherosclerosis, and Atherogenesis

A few words about the nature of the arteriosclerotic process, and the terms that are commonly used in discussing it, may be helpful to the reader in understanding the disease, its complications, and the health problem that it poses.

*Appendices to this Volume (A-G) provide background materials.

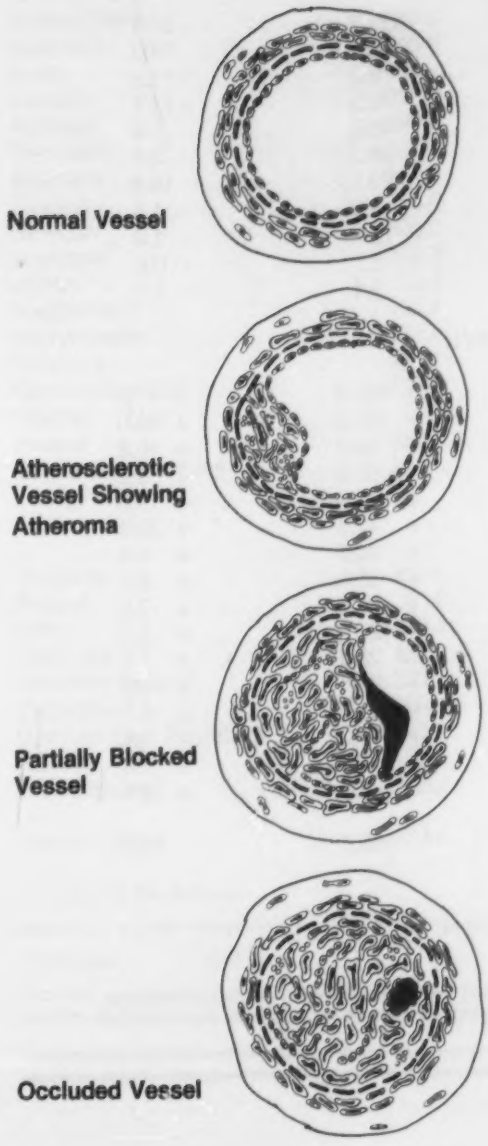


Figure 3. Course of atherosclerotic coronary artery disease, terminating in occlusion of the vessel. Normal vessel (top) and progressive occlusion of the vessel by scarred, thickened plaque and thrombus.

Arteriosclerosis, a synonym for hardening of the arteries, is a term used to describe a *group* of diseases affecting arteries in a particular way.

Atherosclerosis is a specific type of arteriosclerosis that affects large arteries. It is the underlying pathologic condition in most cases of coronary heart disease, aortic aneurysm, peripheral vascular disease, and stroke.

Atherogenesis is the process that culminates in atherosclerosis. In its early stages, the inner layer of an affected artery becomes thickened by deposition of fat, particularly cholesterol, together with an increase in the number of cells in the innermost layer of the artery. Some arteries, even in the same organ, are affected more than others, possibly because of local differences in blood pressure and blood flow. As the deposits of fat and cells enlarge, a reaction to their presence sets in and gradually culminates in scarred and thickened plaques. These plaques protrude into the lumen of the affected artery, hampering blood flow and predisposing to the formation of a blood clot (or thrombus) on the surface, thereby impeding or cutting off blood flow (Figure 4). For a long time, the abnormal vessel wall and the resulting local disturbances in blood flow produce no clinical clues to their presence. But, in time, previously silent atherosclerotic disease may suddenly manifest as a heart attack, a stroke, another life-threatening illness or, all too often, as sudden death.

Because of the clinical disorders that it produces, atherosclerosis—its causes, evolution, prevention, control, and treatment—is the focus of this report.

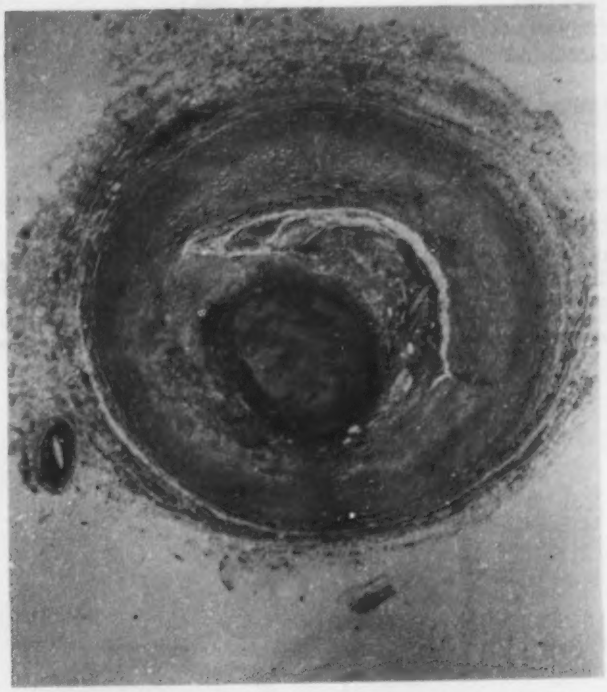


Figure 4. Coronary artery occlusion by an atherosclerotic plaque and a thrombus, resulting in a fatal heart attack (microscopic section).

Table 1. Mortality Rate for Coronary Heart Disease, Men Age 35-74, 1969 to 1977

Country	1969 Rate	1977 Rate	Difference	% Difference
		DECREASE		
United States	864.7	669.5	- 195.2	- 22.6
Australia	843.7	683.1	- 160.6	- 19.0
Canada	703.3	624.1	- 79.2	- 11.3
Israel	653.3	581.0**	- 72.3	- 11.1
Norway	582.9	537.1	- 45.8	- 7.9
New Zealand	773.3	747.1	- 26.2	- 3.4
Japan	126.3	102.6	- 23.7	- 18.8
Belgium	446.1	426.8**	- 19.3	- 4.3
Finland	893.7	878.0**	- 15.7	- 1.8
Scotland	813.7	808.6	- 5.1	- 0.6
Italy	313.0	309.6*	- 3.4	- 1.1
		INCREASE		
Bulgaria	299.3	423.5	+ 124.2	+ 41.5
Poland	186.5	307.7	+ 121.2	+ 65.0
Northern Ireland	782.4	867.1	+ 84.7	+ 10.8
Romania	170.5	237.3	+ 66.8	+ 39.2
Hungary	441.6	499.2	+ 57.6	+ 13.0
Yugoslavia	185.0	227.6	+ 42.6	+ 23.0
Sweden	523.9	560.1	+ 36.2	+ 6.9
Ireland	662.2	697.7*	+ 35.5	+ 5.4
German Fed. Republic	427.3	458.1	+ 30.8	+ 7.2
Austria	428.3	455.3	+ 27.0	+ 6.3
Switzerland	290.4	312.7	+ 22.3	+ 7.7
Netherlands	478.7	500.5	+ 21.8	+ 4.6
France	195.2	206.9**	+ 11.7	+ 6.0
Denmark	566.1	576.3	+ 10.2	+ 1.8
England and Wales	662.1	671.7	+ 9.6	+ 1.4
Czechoslovakia	587.9	590.4*	+ 2.5	+ 0.4
United States	864.7	669.5	- 195.2	- 22.6

ICD 410-414, 8th Revision.

Rates, per 100,000 population, are average of the rates for men age 35-44, 45-54, 55-64, 65-74.

*1975 data. **1976 data.

The data encompass the period 1969-1977 since 1969 was the first year all countries used the Eighth Revision of the International Classification of Diseases and 1977 was the year of availability to the World Health Organization of latest data from most of these countries.

Table 2. Mortality Rate for Coronary Heart Disease, Women Age 35-74, 1969 to 1977

Country	1969 Rate	1977 Rate	Difference	% Difference
		DECREASE		
United States	359.0	261.6	- 97.4	- 27.1
Australia	348.9	263.4	- 85.5	- 24.5
Israel	366.1	301.6**	- 64.5	- 17.6
Canada	276.9	222.7	- 54.2	- 19.6
Norway	199.4	156.0	- 43.4	- 21.8
Denmark	236.0	194.6	- 41.4	- 17.5
Belgium	172.0	149.2**	- 22.8	- 13.3
Finland	286.0	265.7**	- 20.3	- 7.1
Sweden	206.0	186.1	- 19.9	- 9.7
Scotland	338.2	324.4	- 13.8	- 4.1
Japan	63.4	50.3	- 13.1	- 20.7
Switzerland	100.7	90.4	- 10.3	- 10.2
Netherlands	171.4	161.3	- 10.1	- 5.9
Hungary	231.1	223.7	- 7.9	- 3.4
Czechoslovakia	259.5	252.5*	- 7.0	- 2.7
France	70.7	67.9**	- 2.8	- 4.0
Ireland	288.3	287.3*	- 1.0	- 0.3
England and Wales	236.5	236.0	- 0.5	- 0.2
		INCREASE		
Bulgaria	203.8	248.7	+ 44.9	+ 22.0
Poland	56.8	96.0	+ 39.2	+ 69.0
Italy	133.9	171.4*	+ 37.5	+ 28.0
Romania	102.1	130.7	+ 28.6	+ 28.0
Northern Ireland	323.9	333.8	+ 9.9	+ 9.9
Yugoslavia	98.4	106.7	+ 8.3	+ 8.4
German Fed. Republic	141.1	149.3	+ 8.2	+ 5.8
Austria	172.1	175.9	+ 3.8	+ 2.2
New Zealand	300.4	302.4	+ 2.0	+ 0.7
United States	359.0	261.6	- 97.4	- 27.1

ICD 410-414, 8th Revision.

Rates, per 100,000 population, are average of the rates for women age 35-44, 45-54, 55-64, 65-74.

*1975 data. **1976 data.

The data encompass the period 1969-1977 since 1969 was the first year all countries used the Eighth Revision of the International Classification of Diseases and 1977 was the year of availability to the World Health Organization of latest data from most of these countries.

Table 3. Economic Cost of Selected Cardiovascular Diseases, U.S., 1977*

Disease	Direct Cost for Medical Care	Indirect Costs Due to Lost Productivity		Total Cost
		from Illness	from Premature Death	
All Atherosclerotic Diseases	$11,784	$ 4,657	$22,485	$38,926
Coronary Heart Disease	5,547	2,290	17,825	25,662
Cerebrovascular Diseases	2,864	1,545	3,711	8,120
Other Atherosclerotic Diseases of the Arteries	3,373	822	949	5,144
Hypertensive Disease	3,249	2,693	436	6,378
Rheumatic Fever and Rheumatic Heart Disease	399	202	671	1,212
Congenital Heart Disease	118	26	930	1,074
Other	4,298	2,628	4,243	11,169
Total	$19,788	$10,206	$28,765	$58,759

*Millions of Dollars.

Highlights of the Accomplishments of the 1970's

Important advances have been made in the understanding of all aspects of atherosclerosis and of the atherosclerotic diseases.

Fundamental Research

I. Laboratory-Based Research

Molecular and Cellular Phenomena Associated with Atherogenesis

Research in cell and molecular biology has provided much new and exciting information about the cells of the arterial wall. For example, it has been possible to induce changes in cultured vascular cells similar to those observed in experimentally induced atherosclerotic lesions in intact animals, such as nonhuman primates. Fresh approaches, such as cell culture, have made it possible to examine interactions between blood components (for example, lipoproteins, platelets, or hormones) and the individual cells of the arterial wall, and to assess conditions that promote, or reverse, atherogenesis. The use of cultured vascular cells has also made it possible to identify inherited cellular abnormalities that lead to atherosclerosis, to define cellular metabolic pathways for lipids, and to discover factors that regulate the growth of arterial cells. Cell culture methods are improving rapidly and offer great promise for advancing our knowledge.

Hypotheses of Atherogenesis

At least three important hypotheses concerning the etiology and pathogenesis of atherosclerosis have been investigated during the past decade. These are the lipid infiltration hypothesis, the response to injury hypothesis, and the monoclonal hypothesis. Each of these has stimulated the development of new knowledge concerning the role of arterial cells in atherogenesis. For example, the lipid hypothesis has promoted considerable research on the role of the different plasma lipoprotein fractions in atherogenesis. It has also highlighted the potentially important role of high density lipoprotein (HDL) cholesterol as a protectant against, and of low density lipoprotein (LDL) cholesterol as an enhancer of, atherosclerosis. The monoclonal hypothesis has stimulated research that has yielded knowledge concerning the manner in which cells multiply. The response to injury hypothesis stimulated important new research into the biology of the cells of the arterial wall. This research has led to recognition of the importance of the interaction between elements in the blood (lipoproteins, cells) and the cells that line and compose the arterial wall in atherogenesis.

Genetic Substrate of Atherosclerosis

Intensive study of both humans and experimental animals prone to hyperlipidemia and to atherosclerosis has begun to define specific inherited metabolic disorders that account for their susceptibility. Discovery of the inherited cellular defect responsible for familial hypercholesterolemia has greatly increased our knowledge of how cells adsorb and metabolize lipoproteins. Other inherited abnormalities, such as alteration in the structure and metabolism of lipoproteins, in the functions of platelets, or in the character of cells of the arterial wall, are being identified and may explain other instances of genetic hypersusceptibility to atherosclerosis.

Lipoproteins in Atherosclerosis

The importance of the lipoproteins as the cholesterol-carrying substances in the blood has been clarified during the last decade. The role of these substances and their relation to risk factors such as hypertension, smoking, and diabetes are becoming better understood. A better comprehension has been achieved of the dietary influences on lipoproteins, of the regulation of lipoprotein and apoprotein metabolism, the structure of the different lipoproteins and apoproteins, their interactions with cellular receptors, and the process of their derivation from chylomicrons and liver lipoprotein particles. The reasons for cholesterol accumulation in cells and mechanisms that prevent normal cells from accumulating fat have become better understood as a result of these studies. This knowledge gives an improved scientific base for providing dietary advice to individuals with elevated plasma lipids, in order to prevent and control the atherogenic processes.

Thrombosis in Atherosclerosis

Advances in our knowledge of blood clotting factors, platelets, and prostaglandins have stimulated new insights into old theories about how thrombosis is involved in all the stages of atherosclerosis. Studies have demonstrated that platelets, the principal cells involved in thrombosis, are not only involved in this process, but may play a role in the initiation of atherosclerosis. Many constituents of platelets have been

defined, including a factor that can cause cells of the arterial wall to multiply. An understanding of the potential interactions of platelets and cells of the arterial wall promises to stimulate the development of improved methods for controlling and preventing thrombosis, and possibly of preventing the formation of the lesions of atherosclerosis.

Potential for Regression of Atherosclerosis

Many experiments demonstrate that atherosclerosis can be ameliorated after plaques have formed. Plaques formed in nonhuman primates by diet-induced hyperlipidemia became smaller after the hyperlipidemia was reduced by decreasing the fat and cholesterol composition of the diet. These findings have encouraged attempts to reduce plasma lipids as a strategy for preventing progression of human atherosclerosis.

II. Patient-Oriented Research

Diagnosis and Treatment of Myocardial Infarction

Progress has been made in the early detection of acute myocardial infarction (MI) and in the development and assessment of improved methods for its management. These advances include better methods for control of pain and for the prevention and treatment of life-threatening arrhythmias, and new approaches to reduce infarct size and to combat the high risk of death associated with cardiogenic shock.

Surgical Treatment of Atherosclerotic Disease

Progress has been made in the applications of bypass graft surgery. Criteria for this intervention in angina pectoris and other forms of coronary heart disease have been greatly clarified, and the surgical techniques improved. Parallel advances have been made in the application of bypass surgery for cerebrovascular disease and atherosclerotic disease of trunk and peripheral arteries.

Noninvasive Detection of Atherosclerotic Lesions

Progress has been evident in the development of better ways to detect early atherosclerotic lesions and their sequelae in target organs, particularly noninvasive methods (to avoid surgical incision and insertion of catheters), e.g., echocardiography, radionuclide imaging, ultrasound using Doppler, and computerized axial tomography.

Rehabilitation

Progress has been made in the development and assessment of methods, including early ambulation and rehabilitation, for the long-term care of patients with the atherosclerotic diseases.

III. Population-Based Research

Risk Factors

Continued epidemiologic studies have established firmly the quantitative relationships of high blood pressure, serum cholesterol, and cigarette smoking to the risk of coronary heart disease. These are major established risk factors, amenable to prevention and control measures. The prediction of subsequent disease by using these individual characteristics has been extended by applying mathematical analytic techniques. Advances in partitioning plasma lipoproteins have yielded data indicating that LDL is associated directly and that HDL is associated inversely with atherosclerotic disease, that both are affected by diet, and that HDL is also influenced by cigarette smoking, exercise, and alcohol consumption.

Community Intervention

Research studies have demonstrated that it is possible to control risk factors by use of the mass media in entire communities.

Precursors of Risk Factors in Childhood

An effort has begun to assess the precursors of risk factors in childhood. This knowledge is needed because it is now realized that the maximum preventive effect will probably require primary prevention and modification of the risk factors early in life.

Behavioral Characteristics as Risk Factors

Further knowledge of the effects of personality type, stress, and cultural dislocation has emerged.

Decline in Coronary Heart Disease Mortality

The opportunity to examine mechanisms responsible for the decline in coronary heart disease mortality provides a new approach to finding ways to prevent atherosclerotic disease.

Clinical Trials and Demonstration Projects

During the 1970's, with NHLBI sponsorship and support, major clinical trials and demonstration projects were developed to validate findings from fundamental research and assess their applicability for the primary and secondary prevention, control, and treatment of the atherosclerotic diseases. Ongoing major trials are summarized in Table 4.

These efforts represent a critical step in the research process that links the discoveries of laboratory, clinical, and community research with clinical and public health practice.

The studies presented in Table 4 rely on individual participants. They are designed to achieve one of two goals: to prevent the clinical manifestations of disease in persons who are at high risk, or to limit morbidity and mortality in persons who have already evinced evidence of coronary or cerebrovascular disease. In addition to these individual-oriented studies, NHLBI-sponsored community health programs are underway. These include a nationwide health education program concerned with high blood pressure control, and evaluations of the benefits of intensive education and early detection programs in selected communities.

General Technology Transfer

Change in Smoking, Eating, and Exercise Habits

A large fraction of the millions of Americans who have quit smoking, changed eating habits for health reasons, and adopted exercise programs have done so on the advice of their physicians.

Control of Hypertension

A sustained, cooperative effort to control hypertension has resulted in significant progress in the detection and management of this disorder. The National High Blood Pressure Education Program, which played a key role in this effort, involved government, the health professions, and numerous voluntary and public organizations.

Cardiopulmonary Emergency Treatment

Programs have been developed in communities across the country for dealing with cardiopulmonary emergencies. These include coronary care units in hospitals, training in the techniques of cardiopulmonary resuscitation, and special ambulances equipped to transmit electrocardiograms and supply two-way communication to hospitals. These ambulances are staffed with specially trained nonphysician personnel capable of administering antiarrhythmic drugs and initiating defibrillation under supervision of hospital-based cardiologists.

Noninvasive Methods of Detection and Diagnosis

Improvements in noninvasive diagnostic techniques of import for medical and surgical treatment have been noted previously.

Broad Changes in Lifestyles

By 1980, about two-thirds of American families have changed their eating patterns for health reasons. From 1950 to 1978 the per capita consumption of eggs and dairy fats fell about 30 percent. Consumption of visible fats of animal origin fell about 80 percent. For adults age 25 and over, per capita meat consumption has also declined. As a result, intake of saturated fat and cholesterol declined. Consumption of unsaturated and polyunsaturated fat rose moderately. In keeping with these changes in diet, the mean serum cholesterol level of middle-aged U.S. men decreased from about 235 mg/dl in the 1950's and early 1960's to about 210-220 mg/dl in the 1970's.

The proportion of smokers in the adult population has decreased continuously since the 1960's. In 1964, when the *Report to the Surgeon General on Smoking and Health* was published, a majority of men were still cigarette smokers. By 1978, 37 percent were cigarette smokers. The downward trend was similar among adult women, although not as marked. Unfortunately, during the same time interval, the use of cigarettes by teenagers increased.

In the 1970's, millions of American adults began to exercise during their leisure time.

All three changes in lifestyle—diet, smoking, and exercise—were greater among educated than among less educated adults. This observation suggests that health education can be effective in changing lifestyle.

Table 4. Ongoing Clinical Trials Relating to Atherosclerosis Sponsored and Supported by the National Heart, Lung, and Blood Institute

Clinical Trial	Objective	Participants	Status
Hypertension Detection and Follow-up Program (HDFP)	Evaluation of hypertension control to reduce total mortality.	10,940 participants followed for 7 years at 14 centers.	Intervention phase completed in June 1979; now in analysis and dissemination phase.
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)	Primary prevention of coronary heart disease in hypercholesterolemic patients with the cholesterol-lowering drug cholestyramine and diet.	3,810 participants followed for 7 years at 12 centers.	Now in the intervention phase, scheduled for completion in 1983.
Multiple Risk Factor Intervention Trial (MRFIT)	Primary prevention of coronary heart disease by lowering serum cholesterol, reducing blood pressure, and eliminating cigarette smoking.	12,866 participants followed for 6 years at 22 centers.	Now in the intervention phase, scheduled for completion in 1982.
Primary Prevention of Hypertension	Use of nutritional-hygienic means to prevent development of high blood pressure in persons with high-normal pressures, assessed to be prone to hypertension.	200 participants followed for 3 years in 1 center.	Now in the final recruitment and in the intervention phase, scheduled for completion in 1983.
Control of High Blood Pressure by Non-Pharmacologic Means	Use of nutritional-hygienic means to maintain normotension, without medication or with less medication, in hypertensive persons previously receiving drugs for years.	200 participants in 1 trial at 2 centers, and 400 participants in another trial at 4 centers, to be followed for 2 years.	Now in the recruitment and intervention phase; scheduled for completion in 1983.
Systolic Hypertension in the Elderly	Control by antihypertensive drugs of "pure" systolic hypertension in the elderly and prolongation of life.	500 participants in 5 centers, to be followed for 2 years in a pilot phase of this trial.	Detailed planning of a pilot phase for this trial.
Coronary Drug Project (CDP)	Secondary prevention of coronary heart disease with cholesterol-lowering drugs.	8,341 men followed for 5 to 8.5 years at 53 centers.	Initiated in 1965. Intervention completed in 1975. Now in analysis and dissemination phase.
NHLBI Type II Coronary Intervention Study	Lowering cholesterol with the drug cholestyramine and diet in Type II hyperlipidemics, to achieve coronary artery disease regression.	143 participants followed for 5 years at 1 center.	Now in the intervention phase, scheduled for completion in July 1981.
Surgical Control of Hypercholesterolemia	Prevention of myocardial infarction and death by partial ileal bypass surgery in survivors of myocardial infarction.	Over 200 participants have been recruited into this trial, which has a goal of 1,000 participants. Patients are to be followed for 5 years at 4 centers.	Now in the recruitment and intervention phase.

(continued)

Table 4. Ongoing Clinical Trials Relating to Atherosclerosis Sponsored and Supported by the National Heart, Lung, and Blood Institute (continued)

Clinical Trial	Objective	Participants	Status
Aspirin Myocardial Infarction Study (AMIS)	Prevention of myocardial infarction and death with the drug aspirin in survivors of myocardial infarction.	4,524 participants followed for at least 3 years at 30 centers.	Intervention phase completed at the end of summer, 1979; now in analysis and dissemination phase.
Beta-Blocker Heart Attack Trial (BHAT)	Secondary prevention of coronary heart disease with the beta-blocker drug propranolol for persons recovered from acute myocardial infarction.	3,837 participants in 32 centers to be followed for from 2 to 4 years.	Recruitment phase recently completed; intervention phase to continue into the second half of 1982.
Unstable Angina Pectoris Trial	Secondary prevention of coronary heart disease by coronary artery bypass surgery or medical management in patients with unstable angina pectoris.	288 participants followed for 9 years at 9 centers.	Now in the analysis and dissemination phase.
Coronary Artery Surgery Study (CASS)	Treatment of coronary heart disease by artery bypass surgery or medical management in patients with stable angina or history of myocardial infarction.	780 participants entered into this trial to be followed for at least 4 years at 10 centers. The study also includes a registry of 25,400 patients referred for coronary arteriography at 15 centers.	Now in the recruitment and intervention phase, scheduled for completion in June 1981, with followup to extend for 5 years.

State of Present Knowledge of Atherosclerosis

Pathogenesis

The characteristic lesion of advanced atherosclerosis is the fibrous plaque (Figure 5), which appears as a glistening gray mound of tissue on the inner lining of the artery. As the name implies, the fibrous plaque is a mass of fibrous tissue usually surrounding a core of lipid (mainly cholesterol). Fibrous plaques are most frequent and severe in the arteries of the heart, brain, and legs, where they may increase in size enough to obstruct the flow of blood.

Fibrous plaques begin to appear in the arteries of Americans in their twenties. The rate at which they progress and the arteries most severely affected vary widely from one individual to another. They are more extensive and are larger, on the average, in Americans than in persons from the nonindustrialized countries. Their extent and size are closely associated with the rate of heart attack, stroke, and peripheral vascular disease. Consequently, it is generally agreed that clarifying the origin of the fibrous plaque is the key to understanding the cause of atherosclerosis, and that retarding progression of fibrous plaques is basic to prevention of the related atherosclerotic diseases.

The final step that leads to clinically significant reduction in blood flow usually is thrombosis over a fibrous plaque. Alterations in the fibrous plaque itself—breakdown (ulceration) in its covering that separates its core from the blood, or hemorrhage into the plaque—may predispose to thrombosis. Although less well-defined, alterations in the blood may also increase the likelihood of thrombosis over a plaque. Better understanding of these steps in the final episode that causes rapid blocking of an affected artery could lead to preventing some cases of clinical disease, even though advanced atherosclerosis is present. Recently acquired knowledge about platelets, which are intimately involved in thrombosis, may be useful in this regard.

Conditions that are closely associated with more extensive and advanced fibrous plaques are also those associated with higher rates of coronary heart disease, stroke, and peripheral vascular disease. These conditions are the familiar risk factors—hypercholesterolemia, hypertension, cigarette smoking, diabetes, male sex, and age. The varied nature of these conditions that accelerate the process suggests that several mechanisms are involved. In individuals, different combinations of contributing conditions can lead to a similar result.

The most long-standing and widely held concept about the origin of the atherosclerotic plaque is that abnormal amounts of fatty substances, mainly cholesterol, accumulate in the inner lining of the artery. This process is aggravated by a high concentration of serum cholesterol, particularly cholesterol carried in low density lipoprotein. Accumulation apparently occurs concomitant with proliferation of cells of the arterial wall. These cells and their products form the capsule that gives the fibrous plaque its characteristic appearance. The well-established association of severe atherosclerosis and of clinical disease (heart attacks, stroke, peripheral vascular disease) with hypercholesterolemia lends support to the concept, but it does not, per se, explain the associations with other risk factors.

What initiates early fat deposition or cell multiplication is not clear. A current hypothesis is that injury to arterial endothelium is the initiating factor. Whereas a single endothelial injury probably can heal without a trace, repeated injury is more likely to permit greater cholesterol deposition and to stimulate proliferation of muscle cells and connective tissue in the arterial wall. Because many conditions can result in injury to the endothelium, this idea has stimulated the investigation of a variety of new factors that may be involved in or contribute to the initiation or progression of atherosclerosis. The idea provides a possible explanation for the effects of some of the other risk factors, such as cigarette smoking and hypertension. Whatever the other factors may be, it should be remembered that injury is more likely to lead to advanced atherosclerosis if hypercholesterolemia also is present.

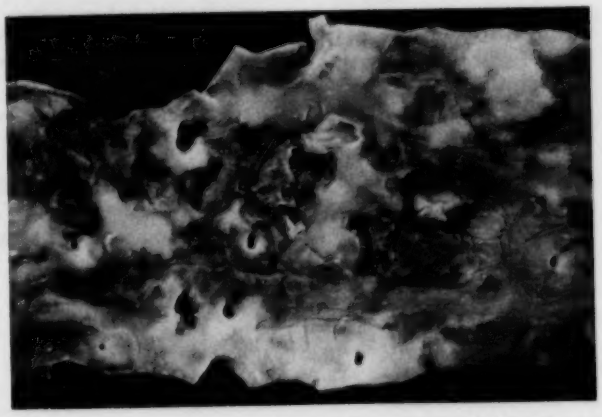


Figure 5. Thoracic aorta with numerous elevated gray fibrous plaques, some of which are ulcerated and covered with thrombi. Dark areas between fibrous plaques are stained fatty streaks.

An important concept that has been accepted only recently is that the growth of an atherosclerotic fibrous plaque to the point of obstruction is not inevitable after it begins. Several experiments with animals have demonstrated that experimentally induced plaques can be arrested and even reversed by lowering blood cholesterol levels. There is limited but encouraging evidence from humans that their plaques also can undergo regression. Enhancing knowledge of the conditions that favor regression of established atherosclerotic plaques in humans is a major research problem.

Clinical Manifestations

The major consequences of atherosclerosis are disorders of the heart, brain, and extremities.

The Heart

Ischemic heart disease, or **coronary heart disease,** is a general term used to identify cardiac disorders resulting from inadequate delivery of blood to the heart muscle. Nearly always, ischemic heart disease is the result of severe atherosclerosis of the coronary arteries. Limitation of blood flow to the heart restricts its supply of oxygen and nutrients as well as its ability to remove waste products of metabolism. The designation "ischemic heart disease" includes angina pectoris.

Angina pectoris is a condition marked by periodic episodes of chest pain, especially during exertion, that result from inadequate coronary blood flow and, hence, an inadequate supply of oxygen to working heart muscle. The dull, sometimes crushing pain under the breastbone that usually characterizes an episode of angina is of relatively short duration—less than 20 minutes—and goes away after a minute or two of rest.

It is often quickly relieved by nitroglycerin or other antianginal drugs. Angina pectoris sometimes occurs at rest, and is then not as readily relieved by nitroglycerin. A few of the antianginal drugs increase the blood supply to the heart by dilating accessory (collateral) blood channels which detour blood around sites of coronary artery obstruction; however, most of them reduce the workload of the heart by lowering blood pressure, and hence its oxygen requirements.

Persons with angina need to learn how to avoid provoking episodes of pain without becoming chronic invalids. The discomfort of angina does not mean that a heart attack or death is imminent. However, they must also learn to identify the features of a heart attack, a disorder which does warrant prompt medical attention.

Most people with angina pectoris are relieved of their discomfort by medication. However, some do not respond to medical management. For those refractory to medical management, coronary artery bypass—a surgical procedure—has come into wide clinical use in the United States during recent years. This procedure uses blood vessels from other parts of the body to construct detours through which blood can bypass narrowed portions of coronary arteries, thereby improving the supply of oxygen and nutrients to the heart muscle. Usually segments of the saphenous (thigh) vein, removed from the patient's leg at the time of operation, are used. In nearly every instance, the blood supply to the heart muscle increases promptly, often accompanied by a dramatic relief of anginal symptoms.

In addition to relief of angina, life expectancy may be increased for patients who have undergone bypass surgery for occlusion of the left main coronary artery. For patients with other predominant sites of coronary artery occlusion, the long-term effects of bypass surgery on life expectancy are less certain.

A new technique (percutaneous transluminal coronary angioplasty) has recently been introduced in the attempt to avoid the major surgery involved in the coronary bypass procedure. It involves the introduction of a cardiac catheter into an obstructed coronary artery, advancing the catheter to the site of obstruction, and inflating a balloon to distend the vessel and relieve the obstruction. This technique is currently being evaluated at a number of different medical centers.

Acute myocardial infarction, or **acute heart attack,** refers to death of heart muscle, usually from the abrupt occlusion of one or more coronary artery branches, often by a blood clot (thrombus) forming on an atherosclerotic plaque (Figure 4). Depending on the location within the heart and the extent of the damage, serious, often life-threatening disturbances in heart rhythm (arrhythmias), acute heart failure, and shock may ensue. If the patient survives the acute episode, the damaged heart muscle is replaced by scar tissue (Figure 6).

Symptoms of acute myocardial infarction generally include severe chest pain, nearly always centered under the sternum and often radiating to the left arm or other sites, such as the point of the jaw, the back, or elsewhere. This pain is seldom relieved by nitroglycerin or other antianginal drugs. Sometimes the pain is accompanied by anxiety, profuse sweating, nausea and vomiting, or loss of consciousness. Although an episode of myocardial infarction usually produces distinctive clinical manifestations, as many as one-third may be asymptomatic, so that its residual effects on the heart are discovered only in the course of a routine electrocardiogram.

A majority of deaths from heart attack occur before the victim reaches the hospital, often because initial symptoms and signs of serious illness were ignored. Indeed, on the average, persons experiencing a heart attack wait 3 hours before deciding to seek help—a hazardous procrastination for a condition in which minutes may make the difference between life and death.

Strategies have been developed to cope with the fact that a heart attack causing the heart to stop or to have a disordered rhythm may be lethal before the person can reach the hospital. Twelve million or more people have had training in cardiopulmonary resuscitation (CPR), a combination of rescue breathing and external cardiac compression which can provide life support when the heart stops, until professional help arrives. The number of prehospital heart attack deaths will decline as increasing numbers of Americans become trained to provide such emergency assistance. In addition, more and more communities are acquiring ambulances or other emergency vehicles specially equipped and staffed to cope with cardiac emergencies.

Figure 6. Heart of victim of myocardial infarct several months after acute episode. Large portions of muscle of the left ventricle (below) were damaged by loss of blood supply due to atherosclerosis and thrombosis of a coronary artery. The dead muscle has been replaced by dense white scar tissue (arrow). Loss of functional muscle caused the left ventricle and left atrium (above) to become dilated and to fail, resulting in death from congestive heart failure.

The threat of succumbing to arrhythmias is reduced once a heart attack patient reaches a hospital's coronary care unit or other intensive care facility. Drugs are available there for the treatment of rhythm disturbances, and some patients with severe arrhythmia or cardiac standstill have been resuscitated by external electrical stimulation. The leading contemporary cause of death among patients hospitalized for a heart attack is cardiogenic shock. In this state, the heart cannot pump sufficient blood for the body's needs, because of massive, and often irreparable, damage to the heart muscle following coronary occlusion. Mortality from cardiogenic shock is approximately 90 percent.

A promising research lead is the observation that damage of heart muscle may be reversible for several hours after an acute heart attack. This prospect is encouraging the development of therapeutic measures designed to restore substantial portions of infarcted muscle to a functional state.

Sudden cardiac death often overtakes people in apparently good health, with no overt symptoms of coronary atherosclerosis. Death is usually due to an arrhythmia, possibly caused by a transient interruption of blood flow to the heart muscle. It occurs so quickly that in most cases it is not possible to apply prompt emergency resuscitation procedures and offer any chance of survival.

Congestive heart failure is usually a chronic condition which involves accumulation of excess fluid in the body tissues (edema), including the lungs, abdominal organs, and limbs. Like cardiogenic shock, it occurs when the heart can no longer pump an adequate amount of blood to meet the normal metabolic demands of the organs and tissues of the body. However, in contrast to the cardiogenic shock that sometimes accompanies an acute myocardial infarction, congestive heart failure is usually gradual in onset and responsive to digitalis and other cardiac support measures. A common cause of congestive heart failure is coronary atherosclerosis that leads to permanent heart muscle damage after one or more heart attacks. Congestive heart failure, however, is not uniquely a complication of coronary atherosclerosis. It may also develop gradually over years if the heart is confronted with an unrelenting and usually increasing circulatory burden imposed by some abnormal cardiovascular condition, such as hypertension or a congenital or rheumatic valvular defect. It may also result from rheumatic inflammation or infections that harm the heart muscle itself.

Symptoms include fatigue on modest exertion or even at rest; shortness of breath when lying down, relieved by getting up or sleeping on several pillows; and swelling of tissues, especially of the lower limbs, due to excess fluid (edema). Extensive accumulation

of fluid in the lungs (pulmonary edema) may be a life-threatening complication of advanced congestive heart failure. Pulmonary edema may occur suddenly when an unusual load, such as unaccustomed exertion or excessive salt intake, is imposed on the failing heart. New methods are under study for reducing the extent and severity of the damage to heart muscle after an acute myocardial infarction; these may help to reduce the incidence of congestive heart failure among patients who have suffered a heart attack.

The Brain

The term "stroke" is applied to the sudden onset of vascular disorders affecting the brain or spinal cord. The prototype clinical manifestations are sudden weakness or paralysis of an arm or leg; disturbance of speech, balance, vision, or memory; or even coma. There are three main causes of stroke: 1) blockage of an artery by atherosclerosis; 2) hemorrhage into the brain because of a rupture of an artery (usually associated with hypertension); and 3) an embolus, often the result of a blood clot from the heart lodging in an artery.

The portion of the brain normally served by the obstructed or ruptured blood vessel is damaged or destroyed, as with heart muscle after an acute heart attack (Figure 7). This, in turn, produces clinical signs and symptoms in the parts of the body normally controlled by the affected brain segment, for example, loss of sensation or paralysis in a limb, slurred speech, or loss of consciousness. The effects may be brief, lasting for only minutes or hours, with full recovery as in a transient ischemic attack, or improvement may occur slowly over days, weeks, or months as in a completed stroke.

Although the treatment of stroke has improved during recent years, a major stroke is about as likely to be lethal as an acute heart attack and is more likely to produce severe disability with consequent lost earning potential and severe socioeconomic impact.

Other Organs and Tissues

Occlusive arterial disease due to atherosclerosis may deprive organs other than the heart and brain of an essential blood supply. The major arteries to the legs are particularly vulnerable (Figure 8). Occlusion of the

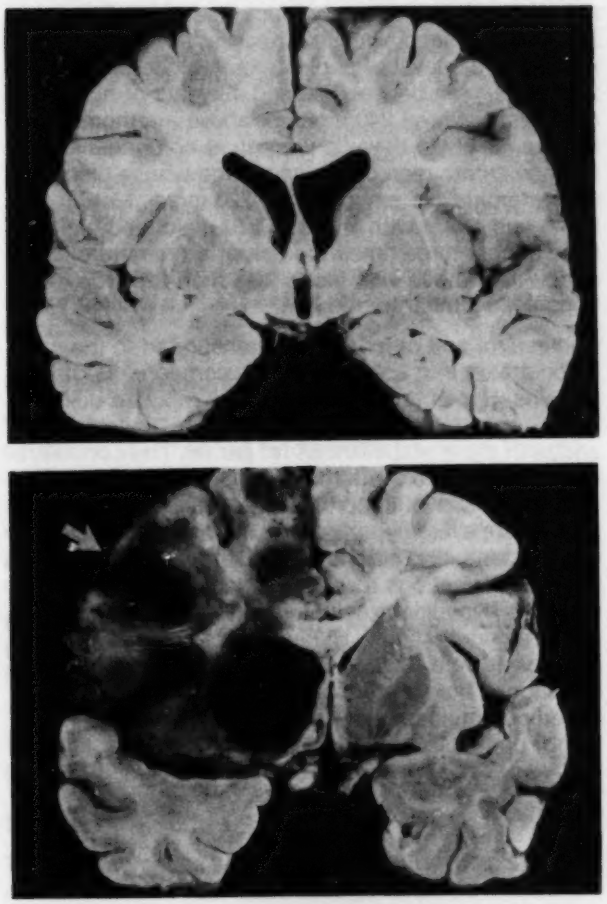


Figure 7. Extensive brain damage resulting after cerebral artery occlusion that resulted in a fatal stroke. Upper: Normal brain. Lower: Extensively damaged brain (left side of photograph).

Figure 8. Extensive atherosclerosis of thoracic aorta (arrow A) with plaques and a clot-filled aneurysm in abdominal aorta below the kidneys (arrows B and C). This lesion obstructs the flow of blood to the lower extremities.

arteries to the legs is responsible for two major clinical manifestations:

Intermittent claudication—transient episodes of pain and muscular weakness usually affecting the calf of the leg during exercise and resulting from an inadequate blood supply. This condition can usually be controlled by medical treatment or, if the response to medical management is inadequate, by surgery to bypass the narrowed arterial segment.

Ischemic gangrene—severe tissue damage or destruction in an extremity due to extreme degrees of blood deprivation. There is often infection and tissue putrefaction. Gangrene may be prevented by surgery, using blood vessel grafts to replace or bypass severely diseased segments of the larger blood vessels in the affected extremity.

In diabetics, obliterative vascular disease of the extremities is a prevalent disorder that is a common cause of premature disability and death. Although atherosclerosis in the diabetic is more aggressive than in the nondiabetic, it is similar in pathogenesis to atherosclerosis in general. Not only the large arteries but also the smaller vessels are narrowed and ischemia develops earlier.

Risk Factors

The concept of risk factors was an outgrowth of findings from prospective epidemiologic studies in the late 1950's. An association was then noted between certain characteristics of individuals who were apparently healthy when first seen and the subsequent incidence of coronary heart disease. The first characteristics identified were a high concentration of cholesterol in the blood (hypercholesterolemia), high blood pressure (hypertension), advancing age, and male sex. Further experience added cigarette smoking, diabetes mellitus, and, particularly in younger people, marked obesity.

The ways risk factors exert their harmful effects have since been extensively investigated in numerous clinical and experimental animal studies. One outcome of these studies has been a greater understanding of how hypercholesterolemia is involved in the development of atherosclerosis and of the progression of the lesion to arterial blockade.

Since risk factors are based on associations uncovered in epidemiologic studies, a risk factor may be a causative agent, a secondary manifestation of an underlying metabolic abnormality, or an early symptom of disease. Much effort has been devoted to identifying risk factors that are causative agents, and that also can be modified. Among the risk factors, the three that best satisfy these criteria are hypercholesterolemia, hypertension, and cigarette smoking. As to the role of a diet high in cholesterol and saturated fat as a risk factor, the relationship is well-established for population groups, and less consistently so for individuals within populations, although recent data are confirmatory for individuals as well. This discrepancy may be due to difficulty in accurately assessing the habitual diets of individuals and the high degree of variability among individuals in the response of blood cholesterol levels to diet. On the other hand, extensive experimental evidence in humans and animals has shown that reduction in dietary cholesterol and saturated fats is associated with a reduction in serum cholesterol levels.

Other characteristics that are less strongly or less consistently associated with the probability of developing coronary heart disease are often referred to as *probable* or *suspected* risk factors. They include physical inactivity, personality-behavior type, and a high concentration of blood glucose without overt diabetes mellitus. Since most of these traits can be favorably modified, clarification of their relationships to the atherosclerotic diseases and their mechanisms of action are important research objectives.

Hypercholesterolemia (High Blood Cholesterol)

The average concentration of cholesterol in the blood plasma of middle-aged American men is presently on the order of 210-220 mg of cholesterol per 100 ml. The risk of premature coronary heart disease and its consequences, especially acute heart attacks, increases rapidly as the level of cholesterol in blood exceeds 220 mg/dl. Men between 40 and 49 years of age with a cholesterol level 240 mg/dl or above are more than twice as likely to develop premature coronary heart disease as are men of the same age whose blood cholesterol levels are less than 220 mg/dl. Men in the same age group with levels of 270 mg/dl and higher have almost three times the risk of a premature heart attack than those with levels less than 220. The relationship is similar for women.

Cholesterol and other fats are transported in the bloodstream in a soluble form as components of lipoproteins. Hypercholesterolemia may reflect a disorder in the proteins transporting the fat (apolipoproteins) and/or in the metabolism of fat per se. The concentration of other blood fats may also be inordinately high from a disorder of lipoprotein metabolism. For clinical purposes, severe hyperlipoproteinemias have been categorized using biochemical and genetic techniques. Distinctions have been made between the common hyperlipoproteinemias in the population and the rare genetic types. Hyperlipoproteinemias may also result from endocrine disturbances and, most commonly, from dietary excesses. These types of hyperlipoproteinemia are all strongly related to the risk of premature atherosclerosis.

One of the several lipoproteins that transport cholesterol—high density lipoproteins—may confer some protection against atherosclerosis: an inverse relationship has been identified between the concentration of HDL cholesterol in the blood and coronary heart disease. Thus, individuals with high levels of HDL tend to have a lower risk of coronary heart disease compared to those with low HDL levels. In contrast, the higher the LDL level, the higher the incidence of coronary heart disease. These observations have led to a reexamination of the interactions of the two lipoproteins with cells of the arterial wall. Although the reasons for the different effects of the different cholesterol-carrying lipoproteins are not yet clear, the information provides new ways of identifying persons at high risk and new prospects for preventing, and even reversing, atherosclerosis.

High Blood Pressure (Hypertension)

As blood pressure rises, so does risk of ischemic heart disease and its complications. The range of normal blood pressures is wide. Even within the "normal" group, risk increases as the upper limits are approached. Usually, blood pressures are expressed as systolic pressure/diastolic pressure; values exceeding 140/90 mm Hg are considered to be hypertensive for adults. Middle-aged persons with a diastolic blood pressure of 90-104 mm Hg or greater (so-called "mild" hypertension) have a risk of heart attack that is about 70 percent higher than that of persons with a diastolic pressure under 80 mm Hg (normal value). Persons with a diastolic blood pressure exceeding 104 mm Hg (moderately severe to severe hypertension) have a risk more than twice that of those with a normal value.

Hypertension is an especially strong risk factor for stroke and, to a lesser extent, for peripheral vascular disease.

Cigarette Smoking

Vulnerability to ischemic heart disease and its complications is enhanced by cigarette smoking. The risk increases in proportion to the number of cigarettes smoked: the pack-a-day smoker runs about twice the risk of a heart attack of the nonsmoker; the two-pack-a-day smoker has about three times the risk of a nonsmoker.

For the pipe or cigar smoker, risk is slightly higher than for the nonsmoker. In ex-smokers, the risk begins to decrease soon after the habit is discontinued, and with time can reach that of nonsmokers.

Smoking is also a very strong risk factor for peripheral vascular disease.

Diabetes Mellitus

The leading cause of death among diabetics is atherosclerosis. Diabetes mellitus is generally identified based on excessive levels of glucose in the blood. The most important determinant of adult-onset diabetes (the most common type) is marked obesity. Diabetes increases the risk of heart disease in all age groups of both sexes. The mechanisms responsible for the increase in risk are unclear. This increased risk is greater among diabetic women than among diabetic men.

Diabetic men between the ages of 45 and 74 have about a 50 percent higher risk of ischemic heart disease and its complications than do nondiabetics in the same age group. In diabetic women of the same age, risk is about two-and-a-half times that of the nondiabetic.

Diabetes is also a risk factor for stroke and peripheral vascular disease.

Obesity

Although marked obesity is a risk factor for ischemic heart disease, at least in early middle age, a great deal of the effect is due to the fact that obesity increases the likelihood of hypercholesterolemia, hypertension, and diabetes. Indeed, diabetes is now established as one of the chief health hazards of the markedly obese state. Obese individuals are more likely to have elevated concentrations of atherogenic lipoproteins and lower levels of HDL in the blood than nonobese persons and their sedentary habits may also contribute to risk.

Obesity alone does not affect longevity unless the individual is markedly overweight.

Family History and Genetic Influences

A family history of premature and often fatal heart attacks is associated with an increase in the risk of ischemic heart disease. This association probably is due to genetic or environmental factors or both. For example, several different abnormal patterns of metabolizing lipoproteins are inherited biologically, and some of these predispose to more severe atherosclerosis and to more frequent ischemic heart disease. On the other hand, familial (rather than genetic) predisposition to atherosclerosis may arise from a common diet and lifestyle. In most individuals, atherosclerosis and its complications are the consequences of interactions between genetic characters and environmental influences.

Exercise

A regular program of sensible, reasonably vigorous, frequent, and sustained exercise can improve physical fitness, appearance, and mental well-being. Much less certain is whether physical activity affects morbidity and mortality from atherosclerosis, and, if it does, by what means.

The lingering uncertainty stems from the difficulty of conducting well-designed population studies involving exercise. Of the few that have been carefully executed to date, some—but not all—have obtained data indicating that physical activity operates independently to decrease the risk of developing clinical complications of atherosclerosis. Despite this inconsistency, it is likely that exercise is beneficial.

Behavior Patterns

Certain patterns of behavior seem to enhance the prospect for developing clinical manifestations of atherosclerosis. There is now extensive evidence indicating that individuals who respond to challenges with great competitive drive, hostility, and impatience (frequently called coronary-prone, or Type A, behavior pattern) are more likely to develop coronary heart disease than individuals who do not respond in this way. Data from a few studies also indicate that major changes in occupation or residence, bereavement, or other stressful life events are associated with increased risk of clinical manifestations of coronary heart disease.

Age

It has long been known that in modern Western industrialized society, atherosclerosis becomes more extensive and more severe with advancing age, and that rates of ischemic heart disease and the other atherosclerotic diseases increase with age. Consequently, in assessing risk of ischemic heart disease, stroke, etc., age is an important factor. However, one of the major advances in research on atherosclerosis has been the recognition that it is not solely determined by age, but is influenced by other conditions as well. Many current research efforts are directed at understanding the process of aging apart from specific disease processes, and these efforts may lead to new insights into how aging affects atherosclerosis, ischemic heart disease, stroke, and peripheral atherosclerotic disease. Meanwhile, although aging is considered to be a risk factor, it cannot be controlled as readily as some of the other risk factors.

Sex

Men are much more susceptible to severe coronary atherosclerosis and coronary heart disease than are women. Differences between the sexes in other clinical manifestations of atherosclerosis are less marked. As yet, the sex differential offers no practical means of preventing atherosclerotic disease, but knowledge of the reasons underlying it is likely to suggest new approaches to prevention and control.

A special aspect of the sex differential is the increased risk of heart attacks and stroke in women who use oral contraceptives, most marked for those also smoking cigarettes. In some women, oral contraceptives increase blood lipids and blood pressure and seem to predispose these individuals to thrombosis. After prolonged use, the increased risk seems to persist, even though the use of contraceptives is discontinued.

Other Risk Factors

The association of other characteristics, such as high concentrations of uric acid in the blood, with ischemic heart disease or stroke, has not been consistent. Certain well-established risk factors, such as electrocardiographic abnormalities or transient ischemic attacks (TIA's), are actually early manifestations of heart or cerebral vascular disease. These are useful in detecting individuals who are in imminent danger of developing overt ischemic heart disease or stroke.

Combinations of Risk Factors

Combinations of major risk factors often are present in the same individual. Usually, the greater the number of coexistent risk factors and their magnitude, the higher the likelihood of clinical manifestations of atherosclerosis.

On the other hand, atherosclerotic disease occurs occasionally in individuals who have none of the known risk factors. This does not disprove the predictive value of the risk factors; it only illustrates the complexity of the disease and shows that it may have multiple causes.

Application of Knowledge

Prevention

The ultimate goal of the national program in atherosclerosis is prevention of the process itself and the associated sickness, disability, and premature death. To achieve this long-range goal, a large research effort operates on several fronts simultaneously: clarification of the nature and pathogenesis of the process, elucidation of predisposing and causative factors, and intervention to safeguard individuals and populations.

Although not all the mechanisms by which the risk factors exert their harmful effect in humans are clear, experience and judgment indicate that the quality of life may be improved, and the lifespan prolonged, by avoiding conditions that are associated with those diseases. This realization has prompted efforts by professional, voluntary, and Federal agencies to minimize risk factors. These efforts include programs to treat hypertension, to eliminate cigarette smoking, to control hypercholesterolemia by diet modification, to dec. e obesity, and to improve physical fitness. Meanwhile, because these measures, although prudent, have not all been proven to reduce disease by controlled experiments in humans, several studies are being conducted to test their effectiveness.

Cigarette Smoking

The association between cigarette smoking and atherosclerotic diseases (particularly coronary heart disease and peripheral vascular disease) is so strong and consistent that little doubt remains that cigarette smoking is a cause of those diseases. Furthermore, persons who cease smoking experience a rapid decline in their risk of atherosclerotic disease. In view of these findings, a controlled clinical trial to test the effectiveness of cessation of smoking in preventing coronary heart disease or peripheral vascular disease has not been considered necessary. Sufficient evidence is in hand to advise all Americans that not smoking is a safe, inexpensive, and effective way to reduce the probability of their developing one or more of the atherosclerotic diseases.

Hypertension

Control of hypertension, including so-called "mild" hypertension, by drugs has been unequivocally demonstrated to reduce total mortality and to reduce the incidence of stroke. Recent evidence indicates that drug treatment of hypertension reduces risk of coronary heart disease. The overall benefits of controlling hypertension are so clear that treatment of hypertension must be included in any program designed to prevent atherosclerotic disease.

When new knowledge makes possible the primary prevention of hypertension, we may reasonably expect that the reduction of hypertension will lead to a concomitant decrease in atherosclerotic disease.

Hypercholesterolemia

Control by Diet Modification

An overwhelming body of evidence accumulated over many years of investigation supports the association between an elevated concentration of cholesterol (especially that in LDL) in the serum and the progression of atherosclerosis. The serum cholesterol (and LDL concentration) of Americans and of people in several other "Western" countries from early childhood are higher than those of persons of many other countries. Although the chain of physiological steps leading from high serum cholesterol concentration to atherosclerosis has not yet been fully defined, there are plausible mechanisms for a causal relationship. The strength, consistency, and coherence of this association has led to the expectation that reduction in the concentrations of cholesterol (particularly LDL) in serum will retard the progression of atherosclerosis and reduce the incidence of clinically manifest atherosclerotic disease.

Nearly 30 years of intensive epidemiological and clinical investigations of humans and an even longer period of animal experimentation also have accumulated convincing evidence that the amount and type of fat and the amount of cholesterol in the diet influence the serum cholesterol concentration. Numerous experiments with humans for limited periods (up to a few years) have shown that the serum cholesterol concentration (LDL) can be reduced in most persons by diet modification, principally by reducing the amount of saturated fat in the diet, with or without replacement of some saturated fat with polyunsaturated fat, and reducing the cholesterol intake. With such diet, reducing the total caloric intake of obese persons sufficiently to reduce adiposity also contributes appreciably to lowering the concentration of total, LDL, and VLDL cholesterol in the serum. At the same time, HDL levels increase. These changes are effective at all ages, including early childhood. Other dietary factors have been shown to influence serum cholesterol, but their effects are less pronounced and less consistent.

Several small-scale clinical trials have tested the effectiveness of preventing clinically manifest atherosclerotic disease by reducing serum cholesterol through diet. The results have been inconclusive, although they have suggested a beneficial effect. It has been proposed that the major reasons for the inconclusive results are that the trials have been confined to middle-aged or elderly adults who would be expected to have already developed atherosclerosis in the course of their lifetimes, the trials have necessarily been limited to a few years, and they have included only a small number of participants. It has not been possible, nor does it appear feasible at present, to test prospectively a modified diet in a controlled trial using large numbers of people, beginning in childhood, youth, or young adulthood, continuing into middle age when clinical manifestations of atherosclerotic disease begin to occur.

With rare exception, voluntary health agencies, scientific and medical professional organizations, and national advisory panels in the U.S., Western Europe, and Australia-New Zealand have concluded over the last 20 years that dietary modification is likely to retard the progression of atherosclerosis and to reduce the incidence of atherosclerotic disease and its complications. Although suggested measures that would effect the dietary change have varied somewhat from one group to another, in general they are similar, i.e., a decrease in total and saturated fat, a moderate increase or unchanged intake of polyunsaturated fat, and a decrease in the consumption of cholesterol-rich foods and total calories. Usually, exercise is also recommended to aid in correcting or preventing obesity. As indicated by dietary surveys and patterns of consumption, substantial segments of the American population already have altered their diets in accordance with these recommendations.

Recently it has been shown that different lipoprotein fractions have different functions and that dietary components may exert selective effects on these specific lipoprotein fractions. This knowledge, when further developed, may lead to stronger physiological links between diet and atherosclerosis; it may also lead to further refinement of the current recommendations for dietary modifications.

There are no known hazards involved *directly* in reducing total fat, saturated fat, or cholesterol intake. Some possible hazard has been attributed to a large increase in the proportion of polyunsaturated fat, but not to the modest increase recommended. The only problems realistically anticipated are those due to inadvertent concomitant changes in other nutrients, such as an increase in salt or a deficiency in minerals or vitamins. These hazards can be avoided by appropriate planning.

NHLBI is actively engaged in a program designed to prevent atherosclerosis and its complications. It has supported many diet trials, has prepared and distributed material describing special cholesterol-lowering diets for severely hypercholesterolemic persons, and has sponsored many conferences, workshops, and advisory panels concerned with nutritional approaches to controlling major risk factors for the prevention of the atherosclerotic diseases. It is anticipated that NHLBI's program in public education will continue to expand.

Obesity

Control of obesity has been included in almost every program designed to prevent atherosclerotic disease. This recommendation is made primarily on the basis of the established association of obesity with diabetes, hypertension, and hyperlipidemia, all risk factors for atherosclerotic disease.

Physical Activity

There is no unequivocal evidence that physical activity alone is effective in the primary prevention of atherosclerotic disease. However, physical activity improves a person's feeling of well-being, and may contribute to controlling weight, blood pressure, hyperlipoproteinemia, and diabetes. Physical fitness is a desirable goal for many reasons, but it has not been proven as effective in preventing atherosclerosis.

Behavior Patterns and Atherosclerosis

The critical element with respect to altering the major risk factors for atherosclerosis is behavior modification. How to go about modifying behavior to further this goal is a key question. Three categories of intervention are currently in use: self-help, community measures, and help by a practitioner. These approaches are described in considerable detail in Volume II.

As noted previously, evidence is available to suggest that certain personality-behavior patterns are possible, or probable, independent risk factors for atherosclerotic disease and its clinical manifestations. Little experience is as yet available in applying this knowledge for purposes of prevention.

Technology Validation and Transfer

In 1972, the Congress mandated that the NHLBI include programs for disease prevention and control through educational activities. The Institute was specifically charged not only with accumulating and validating information, but with ensuring that the new knowledge would be used. This new and expanded role was subsumed under the designation of technology transfer. An Office of Prevention, Education, and Control was created to oversee the execution of this function.

Although the National Heart, Lung, and Blood Institute had engaged in the promotion of health before 1972, its programs gained momentum thereafter. One of its new efforts was the National High Blood Pressure Education Program. Planning and executing this program called for special perspectives, skills, and emphases that were somewhat different from traditional provider roles. For example, a critical element was furthering health goals through marketing techniques and strategies to persuade people to take action to improve their health. Once individuals came for treatment, they also had to be convinced to adhere to the recommended therapy, often a daily dose of medicine for the rest of their lives. Physicians, counselors, nurses, and nutritionists needed to learn better ways to motivate patients and their families to undertake the difficult task of changing personal and family habits. Clearly, to carry out its expanded mandate, the National Heart, Lung, and Blood Institute is obliged to develop new types of health professionals dedicated to prevention through education, behavior modification, and delivery of health services. Among the disciplines that are involved in this activity are medicine, sociology, psychology, industrial engineering, epidemiology, education, marketing, and management.

One important aspect of technology transfer is the avoidance of inordinate delays between scientific discoveries and their application for treatment of disease. Conversely, a serious obligation is to avoid premature translation of research experience and results into clinical practice.

In order to avoid both prematurity and undue delay in the transfer of knowledge for practical purposes, new strategies are needed to promote expeditious, systematic, and reliable evaluation. Currently, the most powerful and sensitive mechanism to evaluate the efficacy, cost, and hazards of a diagnostic, preventive, or therapeutic procedure is the random allocation, controlled clinical trial. The clinical trial is an experiment involving humans, with a sharply defined protocol and a precisely stated intervention. The National Heart, Lung, and Blood Institute is conducting an extensive program of clinical trials dealing with critical issues in the prevention and treatment of heart, lung, and blood diseases. These programs now consume about 15 percent of the Institute's extramural budget. This expenditure is justified by the magnitude of the public health problems that the projects are addressing. The trials that relate directly to atherosclerosis and its complications are listed in Table 4.

Although this technique constitutes a powerful tool, it suffers the disadvantages of being expensive, difficult to organize and administer, and time-consuming. Clearly, alternative and complementary approaches are needed for identifying, evaluating, and introducing new agents, procedures, and measures into the health care system.

Education

The National Heart, Lung, and Blood Institute is committed by congressional mandate to educational activities (National Heart, Blood Vessel, Lung, and Blood Act of 1972, Public Law 92-423). Education is an essential ingredient of technology transfer. In order to implement this function, an Office of Prevention, Education, and Control was created. The nature of health promotion through education is epitomized by the National High Blood Pressure Education Program.

Professional Education

Many types of professional personnel are required to cope with the problem of atherosclerosis and its complications. In addition to the physician and nurse, current clinical practice usually draws upon the skills of social workers, nutritionists, psychologists, and other specialized therapists. Skills in communication and in administration are generally improvised, since contemporary programs of education for health care delivery rarely develop with a team concept in mind. Therefore, the full range of professional skills is assumed by busy physicians or nurses without adequate recourse to other professional help. Progress in health care services requires that this situation be rectified.

Community Education

It was noted above that in order to reach a large target audience, such as those who have hypertension, health professionals are obliged to join forces with experts in the use of the media and with others who are knowledgeable about the organization and delivery of health care. This is a formidable problem for hypertension, which is only one of several major risk factors. The challenge increases markedly when attempts are made to modify several risk factors simultaneously, including those such as smoking, nutrition, or physical fitness, which involve modifications in lifestyle. Community education involves marketing skills that are not ordinarily pictured within the framework of health care delivery. Moreover, since they affect large numbers of people and industry, the economic implications are considerable. Large-scale education of a community is a form of consensus development that may turn into a powerful social and economic force.

NHLBI is currently sponsoring several community demonstration projects. One is under the auspices of the National Research and Demonstration Center (for heart and vascular diseases). This Center is particularly concerned with atherosclerosis and related studies of smoking, nutrition, and hypertension. In addition to its basic research program, the Center has developed a community program which is directed at demonstrating and evaluating the effect of dietary changes on the blood lipids of volunteers from the community. This dietary program has confirmed that in the general population serum cholesterol can be lowered by diet. The Center is now examining various aspects of dietary instruction to determine the most effective program for accomplishing an appreciable decrease in serum cholesterol. Other programs—also heavily dependent on promoting communication between people and providers—are being conducted in the fields of smoking, nutrition, and hypertension.

A second prototype is the Five City Project, designed to test the effectiveness of a health education campaign through the use of multiple mass media. This campaign, begun in pilot form in 1971, is supplemented by a considerable effort to organize the community so that it can achieve skills in self-directed change to reduce cardiovascular risks. This type of study is still at an early stage of development.

Manpower

The arteriosclerosis research endeavor is large and complex. Most of its cost is borne by the Federal Government, particularly by the National Heart, Lung, and Blood Institute, which accounts for three-quarters of the Federal portion. In 1979, the figure for arteriosclerosis-related research in the United States alone, including that supported by pharmaceutical firms, national voluntary agencies, State funds, institutional endowments, and charitable foundations, is estimated to have exceeded $200 million.

Most health-related research, including that in atherosclerosis, is conducted in university medical centers and hospitals, distributed in all or most of the 50 States, and in Federal laboratories, such as those of the National Heart, Lung, and Blood Institute and the United States Department of Agriculture. Collectively, units and centers such as these, with their expert scientists, busy laboratories, and specialized scientific equipment, constitute the front lines of this Nation's research effort for combating and eventually preventing heart attacks, strokes, and the other complications of blood vessels occluded by atherosclerosis.

In the face of the great toll exacted by these diseases in terms of shortened life, sickness, disability, and diminished quality of life, the cost of this research effort is modest. Moreover, continued maintenance of the investment without interruption is essential to sustain the vitality and productivity of the national effort. Of the various elements that comprise the total national resource for research in atherosclerosis, none must be more carefully maintained than the pool of scientific personnel. It is the responsibility of research scientists not only to sense the changing winds of research and to plot the contemporary course for creativity and productivity, but also to train the next generation of scientists.

Because the research enterprise is the key to the Nation's long-term prospects for dealing with atherosclerosis (and other diseases), it is clearly in the national interest to ensure the quality and well-being of the work force.

The Working Group recognized that a steep decline had occurred in the proportion of physicians engaged in research on atherosclerosis. Their view was based on the observation that between 1968 and 1978, a steep decrease had occurred in the number of physicians entering into research. Further evidence along the same line is provided by the Master File of the American Medical Association, in which the number of physicians listing research as their primary activity decreased from 15,400 in 1968 to 8,500 in 1976. The Working Group concluded that this decrease in clinical scientists engaged in research will have a deleterious future effect on research in atherosclerosis.

Conclusions and Recommendations

Perspective

The atherosclerotic diseases, primarily coronary heart disease and stroke, are responsible for almost one-half of all deaths and for more morbidity and disability than any other disease, and have a greater economic impact on the Nation than any other medical problem. Details about the magnitude of this problem appear in Appendix A. Most important, the atherosclerotic diseases affect a large number of persons at the height of their productive lives, many before 65 years of age.

Remarkable strides in preventing, diagnosing, and treating the atherosclerotic diseases have been made during the past decade. The major accomplishments in each of these categories are described in depth in the text of Volume II. In association with the individual gains, mortality from coronary heart disease and the other atherosclerotic diseases has decreased sizably. Despite these gains, morbidity, disability, and mortality from the atherosclerotic diseases remain at epidemic levels.

The national program on atherosclerosis is supported predominantly by the National Heart, Lung, and Blood Institute. During the past decade, scientists have repeatedly warned that this financial support is in serious jeopardy. The resulting uncertainties and limitations, particularly if perpetuated and attended, threaten a serious erosion of the research effort by diverting scientists and physicians to other lines of endeavor which afford greater stability and security. Physicians in particular appear to have responded to these alarms by a decrease in the number entering clinical investigation.

Two measures can be taken promptly to restore confidence in the Federal commitment to research on atherosclerosis:

1. Reaffirmation by the Congress of the broad authorization for NHLBI. This authorization should encompass the full sweep of activities relating to atherosclerosis and its consequences: basic research, applied research, pilot and developmental research, multicenter clinical trials, community demonstration programs, technology transfer to enable widespread application of knowledge, professional and public education, and training to provide the human talents needed for these several aspects of this major health problem; and

2. Authorization by the Congress of a large increase in financial support of the program, to enable implementation of the several broad components at a level commensurate with the need and potential of the 1980's.

Fundamental Research

I. Laboratory-Based Research

Advances in Fundamental Research

Support provided by the National Heart, Lung, and Blood Institute has made possible many important advances in basic research during the last 10 years. Many of these discoveries are already having an impact on clinical care and approaches to the prevention of disease. *In several instances, the initial research that led to these discoveries had no apparent relation to the study of atherosclerosis.* The contributions of diverse areas of research to the study of atherosclerosis have been facilitated significantly by interdisciplinary efforts of investigators with widely different backgrounds and training.

Numerous examples can be cited of important contributions in fundamental research that have enhanced knowledge of atherosclerosis during the past decade. The following examples typify important advances and the necessity for continued support of basic science. They are by no means comprehensive, nor are they presented in order of importance.

Mechanisms by Which Excess Cholesterol Accumulates in Cells

- **Conclusions**

Cells obtained from normal individuals, exposed to a lipoprotein-deficient culture medium, bind low density lipoproteins (the principal atherogenic lipoproteins in humans) to their surfaces by means of high-affinity receptors. This binding precedes the entry of these lipoproteins into the cell interior, and regulates the synthesis and esterification of cholesterol. At high plasma concentrations of lipoproteins this regulation is suppressed; other mechanisms appear to cause the accumulation of cellular cholesterol.

The occurrence of premature coronary heart disease in certain families has been traced to a genetic defect, expressed as a lack of the high-affinity receptor for low density lipoproteins and very high concentrations of low density lipoproteins in blood plasma. A test for high-affinity receptors is currently being used to diagnose this defect and to provide a basis for genetic counseling for carriers of this trait.

- **Recommendation**

The recognition that cells derived from individuals with familial hypercholesterolemia lack a high-affinity receptor for low density

lipoprotein has opened an exciting and entirely new area of research that should lead to new understanding of the manner in which cells control cholesterol metabolism. Research should be continued in pursuit of fundamental mechanisms so that we may understand the determinants of how cells process and metabolize all of the different lipoproteins. The mechanisms by which cells accumulate cholesterol and cholesteryl ester need to be clearly defined to enhance the rational basis for the prevention of disease.

Advances in Methods for Studying Lipoproteins

- **Conclusion**

Contemporary research into the structure and function of lipoproteins has benefited greatly from techniques developed in collateral fields of biology, chemistry, and physics. Among the techniques are ultracentrifugation, electrophoresis, gas and thin-layer chromatography, column chromatography, and spectrometry. Application of those techniques has made it possible to elucidate the structure and function of an increasing number of subclasses of the different plasma lipoproteins, and to unravel some complex interactions and metabolic pathways involved in the synthesis and catabolism of the lipoproteins. Recent developments in techniques such as liquid chromatography and immunoassay hold great promise of continued discoveries, not only in basic science laboratories, but also in their clinical counterparts.

- **Recommendation**

Further development of new biochemical and physicochemical techniques should be supported so that it may be possible to better understand the complex interactions and metabolic pathways involved in the synthesis and metabolism of lipoproteins.

Diet and Atherogenesis

- **Conclusion**

In recent years, biochemists, nutritionists, and other scientists began working with clinical investigators and epidemiologists to examine the effects on lipoprotein fractions of specific dietary constituents such as cholesterol, fatty acids, and proteins. The results of these examinations suggest that each dietary component may have a characteristic and specific effect on plasma lipoprotein patterns. Combined with the knowledge developed from investigations regarding the metabolism of lipoproteins and the interactions between cells and lipoproteins, this information should further clarify the relationship between diet and atherogenesis.

- **Recommendation**

Links between diet and atherogenesis should be further clarified. Support should be provided for additional research on diet and atherogenesis, so that it may be possible to enhance knowledge about effects at the cellular, tissue, and organ level.

Platelets in Atherogenesis

- **Conclusion**

The participation of platelets in thrombosis has been more clearly defined. Mechanisms have been elucidated by which platelets are stimulated to adhere and aggregate, and to release their contents. This knowledge has led to new means of inhibiting the undesirable aspects of platelet function, new clinical approaches to the prevention of thrombosis, and to the development of methods for identifying the involvement of platelets in thrombosis. The participation of platelets in the initiation of atherosclerosis in experimental animals has been established. The discovery that platelets contain a mitogen that stimulates multiplication of smooth muscle cells in culture may be important in atherogenesis. This mitogen, the platelet-derived growth factor, was identified as a result of studies of the control of cell growth in culture. These new insights have prompted, in turn, a search for medical strategies by which platelet stimulation might be inhibited or neutralized in an effort to slow the process of atherosclerosis.

- **Recommendation**

Recent research has established a role for platelets not only in thrombosis, but in atherogenesis. Support should be provided for studying interactions between the platelets and the arterial wall, since understanding these reactions may be important in defining the conditions responsible for their occurrence. Further research in this area could lead to information that might be useful in diagnosis, treatment, and prevention.

Prostaglandins in Atherosclerosis

- **Conclusion**

An important discovery in the last 10 years has been that prostaglandins strongly influence the behavior of the arterial wall and of cells in the blood traversing the arterial lumen. Prostaglandins, particularly thromboxane A-2 and prostacyclin, are thought to be the most potent substances known for aggregating and dispersing platelets. The clinical usefulness of these substances requires further study. In fact, prostacyclin is already being tested in clinical trials. Moreover, some long-available medications, recently shown to modify prostaglandin metabolism, are now being examined for their potential in preventing the complications of atherosclerosis.

- **Recommendation**

Further pharmacologic research will help to elucidate the roles of these and other potentially active compounds in the metabolism of the arterial wall and of circulating blood cells. Information on the mechanisms by which these substances alter the response of cells could lead to better understanding of their clinical usefulness.

Experimental Models of Human Atherosclerotic Diseases

• Conclusion

Experimental pathologists, collaborating with basic scientists in other disciplines—biochemistry, physiology, immunology, surgery, virology, and cell biology—have developed a variety of techniques for producing arterial injury and for influencing arterial metabolism. These models of arterial injury and repair have helped to explain how endothelial cells, smooth muscle cells, macrophages, and connective tissue function in the progression and regression of lesions of atherosclerosis. These investigations have resulted in new hypotheses of atherogenesis that could lead to improved methods of both prevention and treatment.

• Recommendation

Since it has become clear that coronary heart disease is the result of a multifaceted process, the development of multiple approaches to study the initiation, progression, and regression of the lesions of atherosclerosis in a wide range of experimental animals, including nonhuman primates, should be further supported. Additional models of atherosclerosis should be developed, and those that have been studied should be extended to utilize every avenue to further study lesion progression and regression.

Relationship Between Cells of the Arterial Wall and Atherosclerosis

• Conclusion

The development of techniques for growing cells from the arterial wall in tissue culture and for retaining their phenotype represents an important breakthrough in cell and molecular biology. With this approach, it has been possible to study the metabolism of arterial endothelial and smooth muscle cells. Factors that control the growth of these cells and their capacity to form connective tissue macromolecules and metabolize lipids can now be studied and modified. This approach should permit an analysis of the behavior of human arterial wall cells in relation to factors associated with the pathogenesis of atherosclerosis. The development of new techniques in electron microscopy has permitted the morphological localization of sites of many important metabolic activities at the surfaces of cells. Such techniques have been used to study the regulation of endothelial permeability, as well as basic transport processes in cells.

• Recommendation

Further support should be provided for approaches that utilize the techniques of cell and molecular biology in studying the problems of atherosclerosis. Techniques such as cell culture and electron microscopy have begun to provide information that will permit the development of correlative data between alterations at the cellular level and changes that occur in whole organisms in the course of development of the disease. The opportunities to correlate studies of cells in culture with the alterations that occur in cells, tissues, and organs of the intact animal may permit these observations to be related to changes that occur in man. These new approaches permit studies of endothelial cells, smooth muscle cells, macrophages, and platelets, all of which are intimately related to the process of atherosclerosis. Further support of research in these areas continues to be important.

• General Recommendations

The foregoing examples illustrate the beneficial effects from the interaction of scientists working in different areas of research. Because the process of atherosclerosis is complex and multifaceted, and because interdisciplinary approaches are being rapidly incorporated into its investigation, one cannot validly select specific areas of basic research that may contribute more than others to the solution of the problem. It is therefore essential that the National Heart, Lung, and Blood Institute continue to support a wide area of research in the biomedical sciences, as well as research designed to test specific hypotheses of atherogenesis. Inherent in this activity is the probability that exploration of each field will continue to expand understanding of atherogenesis, as has occurred during the last decade. In addition, each development in a given field has the potential of accelerating research in other areas.

Because of the importance of fundamental research and elucidation of information leading to prevention of atherosclerosis, special provision should be made to attract bright young investigators into the basic sciences related to this disease process.

Because of the catalytic effects of epidemiology and clinical medicine on laboratory research in atherosclerosis and the urgent need to advance strategies for prevention of atherosclerosis, collaborative interplay among laboratory scientists, clinical investigators, and epidemiologists should be encouraged.

II. Patient-Oriented Research

Myocardial Ischemia and Angina Pectoris

• Conclusion

Angina pectoris remains a leading cause of morbidity and disability in patients with coronary heart disease despite advances in pharmacologic management by beta-adrenergic blockade and nitrates. Severe coronary atherosclerosis is the usual underlying cause, but coronary vasospasm is also a cause of variant angina pectoris and pain occurring at rest. However, whether vasospasm causes

exertion-induced ischemia, unstable angina pectoris, and acute myocardial infarction is not known. Other possible causes of myocardial ischemia are platelet aggregation, prostaglandin stimulation, abnormalities in coronary artery anatomy, and lack of collateral coronary artery circulation.

• **Recommendation**
The causes and mechanisms of myocardial ischemia at rest and unstable angina pectoris should be further investigated in patients with this syndrome, and animal models of myocardial ischemia should also be utilized for this purpose. Methods for recognizing painless myocardial ischemia and for studying the relation of ischemia to electrical instability of the heart would be helpful in diagnosis, treatment, and research. Factors controlling the development of coronary collateral circulation also need to be elucidated. Further investigation into alternate, or adjuvant, pharmacologic therapy, such as calcium blocking agents and platelet aggregation inhibitors, should be initiated.

Myocardial Infarction

• **Conclusion**
Acute myocardial infarction continues to be a massive cause of sickness, disability, and death in the United States. The medical management of this condition has improved, but better knowledge of its mechanisms should lead to further improvements in therapy. The factors which lead to abrupt narrowing or occlusion of an atherosclerotic coronary artery and the determinants of irreversible myocardial cell damage are not well-defined. Unknown are the cellular mechanisms that trigger ventricular fibrillation and lead to sudden death—the leading cause of out-of-hospital death. Progress has been made in measuring ischemic and infarcted myocardium, but improved methods are needed to evaluate treatments to reduce heart muscle damage. Better methods of predicting risk of recurrence during the first year after acute myocardial infarction are needed to improve the design of therapeutic trials.

Drug therapy may reduce mortality during the first year after myocardial infarction. Surgical treatment has improved survival in some complications of acute myocardial infarction, including mitral regurgitation, ventricular septal defect, ventricular aneurysm, and refractory dysrhythmias. A major continuing problem in about 10 percent of patients with acute myocardial infarction is cardiogenic shock. Diastolic augmentation by intra-aortic balloon pumping or emergency coronary artery bypass grafting may be useful in cardiogenic shock, but the treatment of this complication, together with the surgical treatment of life-threatening dysrhythmias, needs further study.

• **Recommendation**
Research should be continued on processes responsible for abrupt coronary artery occlusion, factors producing electrical disturbances during severe ischemia, and determinants of irreversible damage to heart muscle by coronary occlusion. Criteria should also be developed for identifying patients at varying risks of death and reinfarction during the first year after acute myocardial infarction. Clinical trials should be conducted to identify the optimal medical and surgical treatment for heart failure and shock complicating acute myocardial infarction.

Sudden Cardiac Death

• **Conclusion**
Sudden cardiac death remains a major public health problem. Most victims of sudden cardiac death have extensive coronary atherosclerosis. Persons who have recently had a myocardial infarct and survivors of cardiac resuscitation are at increased risk of sudden death, but other cardiovascular determinants of high risk for individuals in the general population are not yet well identified. Autonomic nervous system activity, delays in impulse conduction within the heart, and single premature beats may occasionally trigger lethal dysrhythmias.

Coronary bypass surgery reduces the incidence of sudden death in patients with left main coronary disease, and also is beneficial for a few patients with serious ventricular dysrhythmias. Clinical trials are now under way to test beta-adrenergic blockade and various antiplatelet drugs in prevention of sudden cardiac death. New nontoxic antidysrhythmic drugs are needed. Public education and emergency care systems in some communities have resulted in improved survival rates for victims of heart attack.

• **Recommendation**
Research should be aimed at better characterization of persons with coronary heart disease (with and without symptoms) who are at high risk of sudden death or other coronary events within a short time. Intervention trials to test potential preventive measures should be established. The Coronary Artery Surgery Study Registry should be useful for improved identification of high-risk persons. The significance of ventricular premature beats in predicting sudden cardiac death should be clarified. Research to find the mechanisms underlying dysrhythmias in ischemic heart disease should be continued. Surgical methods of treating intractable dysrhythmias should be explored.

Coronary Artery Bypass Graft

• **Conclusion**
The coronary artery bypass graft operation has become an established method for relieving anginal pain and, in some patients, for extending length of life. Surgical results have improved, with increased long-term graft patency rate, and reduced operative mortality now in the range of 1 to 2 percent in many centers. More effective methods have been developed to protect the heart during

the operation, and noninvasive techniques for evaluating cardiac function and coronary circulation postoperatively are finding increasing application. Improved methods are needed for maintaining long-term patency of vein grafts.

- **Recommendation**

Research should be continued to assess the results of myocardial revascularization by coronary artery bypass grafts. Methods to preserve the myocardium before, during, and after the operation should be improved. Additional methods to prevent graft occlusion also should be developed.

Exercise, Electrocardiographic Stress Testing, and Rehabilitation

- **Conclusion**

Apparently healthy individuals who have an abnormal electrocardiographic (ECG) exercise test have a higher risk of developing clinical coronary heart disease than those with a normal response. However, a positive exercise test alone does not predict increased mortality over the short term, in either asymptomatic people or patients with angina pectoris. Improvements in exercise ECG technology for screening appear feasible, and other noninvasive tests to detect regional ischemia or left ventricular function abnormalities can further enhance predictive value.

The long-term effects of physical conditioning on the heart remain to be defined. There is little information on the effects of exercise on hearts prone to ischemia, and the effects of exercise on atherosclerosis and manifest coronary heart disease are not known. Because of multiple confounding variables, clinical trials to test the effects of exercise on coronary heart disease do not appear to be feasible.

Early ambulation after acute myocardial infarction has been widely applied since the deleterious effects of prolonged immobilization were established. However, little is known about the physiologic effects of early ambulation on the heart and circulation following acute myocardial infarction, and more knowledge is needed about the relative merits of specific rehabilitative programs.

- **Recommendation**

Research is needed to determine whether exercise affects stress-induced myocardial ischemia or atherosclerosis, and if so, how it produces those effects. Noninvasive methods for diagnosing coronary heart disease should be improved, and the predictive value of standardized ECG exercise testing alone and in combination with other methods should be clarified. Large-scale, prospective clinical trials on the role of exercise in the prevention of cornary heart disease are not recommended because of difficulties in study design. Noninvasive techniques should be used to assess the cardiocirculatory effects of early ambulation after myocardial infarction.

Methods of Diagnosing Atherosclerotic Lesions

- **Conclusion**

The method now used most widely for identifying atherosclerotic plaques in the coronary, cerebral, and peripheral arteries is x-ray imaging after injection of a radioopaque contrast material. This method is costly and its accuracy is limited. Several promising new techniques are being developed, and some are in early stages of clinical application. These techniques are ultrasound, computerized x-ray tomographic imaging, nuclear magnetic resonance, and other methods to produce images of arterial lesions. Some techniques need extensive development; others need only systematic evaluation in clinical practice. The efficient application of many new surgical procedures and the evaluation of potential preventive regimens would be aided greatly by the availability of an inexpensive, safe, and accurate noninvasive method of identifying atherosclerotic plaques in arteries of the heart, brain, or legs.

- **Recommendation**

Development and evaluation of noninvasive methods of assessing atherosclerotic lesions in the coronary, cerebral, carotid, and peripheral arteries should be continued and intensified. Techniques that are ready for clinical application, such as ultrasound imaging with B-mode or Doppler systems, should be subjected to rigorous evaluation before their use becomes widespread.

Methods of Diagnosing Ischemic Tissue Damage

- **Conclusion**

Present methods for identifying ischemic lesions of the heart and brain are indirect and are not sufficiently accurate to guide available treatment and to evaluate new forms of treatment. For example, it would be desirable to differentiate between potentially reversible areas of ischemic injury in the heart or brain and irreversible areas of necrosis or scarring. Several new applications of radionuclides, ultrasound, x-rays, and nuclear magnetic resonance show promise in identifying viable and necrotic myocardium.

- **Recommendation**

Development of noninvasive methods of detecting and measuring blood flow, collateral circulation, tissue injury, and tissue metabolism in the heart and brain should be continued and intensified.

More work is needed on measurement of collateral blood flow in the heart, and on the relationship of collateral circulation to the pathogenesis of angina pectoris and infarction. Better methods should be developed to measure regional blood flow and tissue

metabolism in the heart and brain for detecting obstructive vascular lesions, studying the local effects of environmental factors, and evaluating new medical and surgical methods of treatment.

Percutaneous Transluminal Angioplasty

- **Conclusion**

Percutaneous transluminal angioplasty is a new method of dilating obstructive atherosclerotic lesions in the coronary arteries and arteries of the legs. However, the criteria for selecting patients for whom this procedure is beneficial are not clear, and its long-term, potentially deleterious effects have not been thoroughly studied.

- **Recommendation**

Evaluation of immediate and long-term effects of percutaneous transluminal angioplasty in the treatment of coronary artery disease and peripheral vascular disease should be continued. Long-term monitoring by the NHLBI of percutaneous transluminal angioplasty should be maintained.

Cardiac Transplantation

- **Conclusion**

Progress in human cardiac transplantation in a few centers has led to results equal to those of renal transplantation from unrelated donors. In the single institution carrying out an active cardiac transplant program during the past decade, 70 percent of the carefully selected patients survived 1 year, and 5 percent died each year thereafter. Many long-term survivors have a normal capacity for physical activity and resume active employment. Results currently achieved, however, approach the limits that can be expected with the constraints of current techniques of immunosuppression. Ultimately, the widespread application of cardiac transplantation depends on progress in immunology.

- **Recommendation**

The major support for research in cardiac transplantation should be in cellular immunology. Clinical studies should be continued at the present level.

Artificial Heart

- **Conclusion**

While artificial heart programs have been active for nearly two decades, clinically applicable advances have been made only with temporary left ventricular assist devices, particularly the intra-aortic balloon. This device is now widely used in treating cardiogenic shock and in relieving intractable angina pectoris. It is unlikely, however, that an implantable permanent left ventricular assist device will see widespread clinical applications within the next 5 years.

- **Recommendation**

Research on an implantable mechanical circulatory assist device should continue at the present level of effort.

Peripheral Vascular Disease

- **Conclusion**

Peripheral arterial insufficiency due to atherosclerosis is frequent, particularly in males. It is related to the same risk factors as those for coronary heart disease, i.e., cigarette smoking, hypertension, hyperlipoproteinemia, and diabetes mellitus. Cigarette smoking and diabetes are particularly strong risk factors for peripheral vascular disease. How diabetes contributes to the disease remains unanswered. As with coronary heart disease, long-range prevention depends on the prevention of severe atherosclerosis.

New therapeutic efforts for the management of peripheral arterial insufficiency are being introduced. These include the use of transluminal angioplasty for the treatment of stenoses of the large and medium-sized arteries. Initial reports on the use of prostaglandins are encouraging but need validation. Surgical grafting remains the major method of treatment. All forms of treatment will be greatly aided by the availability of noninvasive diagnostic methods, some of which are now ready for clinical application.

- **Recommendation**

Development and testing of improved noninvasive methods of detecting atherosclerosis in peripheral arteries should be continued. The effectiveness of transluminal angioplasty and of prostacyclin in treating peripheral vascular disease must be evaluated. Synthetic grafts should be improved. Clinical trials of preventive regimens should include assessment of atherosclerosis in arteries of the legs, since these are more accessible than the coronary arteries.

Cerebrovascular Disease

- **Conclusion**

A dramatic decline in mortality from cerebrovascular disease (stroke) has occurred during the last 10 years. Programs for professional and public education in primary prevention and risk factor reduction, particularly control of hypertension, have contributed to this decline. It seems likely that secondary preventive measures, such as recognizing the significance of transient ischemic attacks and asymptomatic cervical arterial bruits and the institution of proper measures for their management have also contributed to this decline. It is not clear whether the reduction of mortality from stroke has been associated with a change in the incidence of new stroke or a decrease or increase in the number of disabled survivors.

- **Recommendation**

Accurate determination of incidence and prevalence of strokes must be made, in conjunction with data on stroke morbidity and mortality, if the socioeconomic effects of this crippling disease are to be assessed.

• **Conclusion**
Investigations of the effect of atherosclerosis upon brain function have been limited by lack of appropriate animal models. The recent development of experimental cerebral atherosclerosis in nonhuman primates, coupled with new ultrasound techniques for quantifying the progression of atherosclerosis over time, provides new prospects for the study of the possible effect of interventions. If successful, these techniques could be applied to human atherosclerosis.

• **Recommendation**
Further attention should be paid to developing suitable animal models. Moreover, efforts should be intensified to develop techniques for noninvasive imaging of arteries supplying the brain in animals and in man.

• **Conclusion**
Since the 1971 Arteriosclerosis Task Force Report, new techniques, particularly computed cranial tomography (CCT) and positron emission tomography (PET), have made it possible to delineate the effects of atherosclerosis on the brain. When coupled with arteriography, these systems provide a detailed map of the anatomy of the arteries (arteriography) and brain (CTT), and of brain metabolism (PET). Together they give a precise anatomical correlation of lesion with clinical expression of cerebral atherosclerosis. Disturbed metabolism not only can be identified, but appropriate intervention can be instituted to limit lesion size and reverse the process. Nuclear magnetic resonance (NMR) systems are a promising new departure. They are still in the early phase of development but offer the prospect of better metabolic assessment by providing rapid, repeatable measurements in local regions of the brain.

• **Recommendation**
Because of the enormous potential of positron emission tomography, nuclear magnetic resonance, and computerized cranial tomography for investigating the effects of atherosclerosis upon the brain, exploration of their potential for the diagnosis, treatment, and prevention of the complications of atherosclerosis should be encouraged.

•**Conclusion**
Since the first Task Force Report, noninvasive methods utilizing radioactive xenon inhalation for determination of regional cerebral blood flow have been perfected. Using this approach, limb movement, speech, mentation, and reading have been shown to affect the distribution of brain blood flow in characteristic ways and that distribution is altered by cerebrovascular disease.

•**Recommendation**
Further research is needed to clarify the normal patterns of cerebral blood flow, how they are affected by atherosclerosis and its complications, and the consequences of surgical and medical interventions.

•**Conclusion**
Individuals who manifest a transient ischemic attack are also at high risk for subsequent development of clinical coronary heart disease. Because the cervical vessels are readily accessible for noninvasive evaluating, the possibility exists that demonstrable atherosclerotic disease in these vessels may be useful as an index of clinically important atherosclerosis in other vascular beds.

•**Recommendation**
Population-based studies should be undertaken to determine the relationships between severity of atherosclerotic lesions in different arterial beds, and whether atherosclerotic disease in an accessible artery such as the carotid can be utilized as a predictor of disease in the coronary circulation.

III. Population-Based Research

Experiments of Nature

• **Conclusion**
Variations in frequency of the atherosclerotic diseases in different countries and regions, changes in frequency that occur when populations migrate, and the recent decline in mortality in the United States provide opportunities to study the causes of these diseases. Unfortunately, it has not proved easy to identify a uniform pattern of precursors in all populations. Each clinical event, in the form of a heart attack, stroke, or a lack of circulation in an extremity, is the culmination of a complex interplay among diverse influences: age, gender, ethnicity, dietary and serum lipids, blood pressure, cigarette smoking, diabetes, obesity, stress, and probably other elements as yet undefined. In some individuals and populations, one set of factors may predominate; in others, a different set of influences may be overriding. Full advantage has not yet been taken of the experiments of nature, which cannot be duplicated in the artificial setting of the laboratory, to learn how these factors interact in different environments to cause atherosclerotic disease. Such knowledge would be useful in improving preventive regimens.

• **Recommendation**
Intensified research efforts are needed to define and to explain the major differences in the frequency and severity of the atherosclerotic diseases—ischemic heart disease, stroke, and peripheral vascular disease—in different social, ethnic, regional, and national groups, and over time.

Decline in Cardiovascular Mortality

• Conclusion

The continuous and substantial decline in mortality rates from coronary heart disease in the United States is probably due to changes in multiple determinants of the disease. Identifying the mechanisms responsible for the decrease may help to accelerate the decline in coronary heart disease and to develop insights applicable to the control of other major diseases in modern industrialized societies. Because of the continuing high toll of the atherosclerotic diseases in terms of premature illness, disability, and death—despite the decline in the death rates—clarification of the bases for the decline in mortality requires urgent attention.

• Recommendation

Analyses of the decrease in mortality are needed to ascertain its patterns in various occupational, ethnic, and social groups; its relation to trends in severity of coronary atherosclerosis at post mortem; data on atherosclerotic disease mortality trends demographically and over time; and utility of underlying and contributing causes of death (multiple-cause mortality data) for enhanced descriptions of mortality patterns.

Surveillance systems should be organized in selected communities to monitor long-term trends of incidence of nonfatal and fatal disease. These trends should be related to changing lifestyles and risk factors, and to changes in treatment of the atherosclerotic diseases, in order to assess whether the overall incidence of the disease is declining, the case fatality rate is decreasing, or both, and to evaluate whether the severer forms of the disease are becoming less frequent.

Epidemiology and the Pathogenesis of Atherosclerosis

• Conclusion

Advances in laboratory-based research with respect to the nature of atherosclerosis have opened new avenues for epidemiological exploration. Epidemiological studies have also succeeded in identifying certain factors that are associated with an increased risk of developing atherosclerotic disease.

• Recommendation

Research should be encouraged to clarify links between the risk factors identified in studies of populations and the mechanisms of pathogenesis of atherosclerosis.

Childhood and Atherosclerosis

• Conclusion

Insights provided by research in the 1970's with respect to defining and measuring the relations among lifestyles, risk factors, and the development of atherosclerotic disease have been applied in a variety of programs directed toward preventing atherosclerotic disease in adults. Because patterns of diet, smoking, and exercise are established in childhood and adolescence, maximum benefit is apt to be achieved when interventions are initiated as early as possible in the evolution of the disease.

• Recommendation

Long-term research activities should be increased with respect to the development of risk factors early in life, the relation between these events and illness in adult life, and means in young people of reducing future risk.

Behavioral Patterns and Risk of Disease

• Conclusion

One of the most complex problems in atherosclerosis is the association of risk of disease with human behavior, personality, and social and cultural influences. Principles of conditioning to social learning have been shown to be operative in behavior patterns which influence cardiovascular risk factors, adherence to medical regimens, and outcomes of treatment for cardiovascular disease. Although behavioral characteristics are clearly important in determining habits of diet, smoking, and exercise, they also exert independent effects through mechanisms that are not as clear as are established biochemical and physiological pathways of atherogenesis.

• Recommendation

Research on influencing and modifying behavior should be encouraged. Improved objective measures of behavior and social factors need to be developed and linked to quantitative measures of physiological and biochemical risk factors for atherosclerotic disease.

Possible Unrecognized Risk Factors

• Conclusion

Assessment of combinations of risk factors has proved useful for predicting the presence of severe atherosclerotic disease in persons who are ostensibly well. Although the assessment does sort people into a wide range of groups according to risk, errors of classification do occur. One inference from the misclassification is that other individual and environmental determinants of atherosclerotic disease may remain to be discovered.

• Recommendation

Opportunities should be afforded for new directions in research on currently unidentified risk factors in the etiology and pathogenesis of atherosclerosis.

Prevention

Primary Prevention of Coronary Heart Disease

• **Conclusion**
The marked and continuing decline in mortality rates from coronary heart disease and the other atherosclerotic diseases in the 1970's lends support to the concept that the epidemic onslaught of these diseases can be controlled and prevented. It underscores the emphasis on primary prevention advocated in the 1971 Report by the NHLI Task Force on Arteriosclerosis.

In the 1970's, the United States led the industrialized countries of the world both in stimulating preventive programs and in the decline in mortality rates. Emphasis on prevention should be maintained and extended because of the continuing high sickness, disability, and death rates from these diseases.

NHLBI, with only limited funds available for this aspect of its work, has contributed significantly to the initial preventive efforts. With reasonable resources, it could contribute much more.

• **Recommendation**
In keeping with its broad authorization and charge, encompassing research and its applications, NHLBI should increase its activities at all levels for the primary prevention of coronary heart disease, stroke, and other atherosclerotic diseases. Funds necessary to implement this central strategic objective should be appropriated.

Primary Prevention of High Blood Pressure

• **Conclusion**
Among the major established risk factors, hypertension is of critical importance. In the early 1970's, after completion of the Veterans Administration trial on antihypertensive treatment, NHLBI assumed the leadership in the next phases of research and development on hypertension. It launched both a clinical trial (the Hypertension Detection and Follow-up Program) and a control program (the National High Blood Pressure Education Program).

The Hypertension Detection and Follow-up Program (HDFP) has now been completed. It has demonstrated that vigorous, sustained antihypertensive treatment will lower mortality rates for people with high blood pressure, including large numbers with so-called mild hypertension. These results also suggest that millions of Americans with "modest" elevation of blood pressure would benefit by pharmacologic intervention when other measures, e.g., diet and exercise, fail to bring blood pressure to adequate control.

Of even greater potential importance is research on the *primary prevention of high blood pressure*, e.g., by control of obesity, dietary salt restriction, correction of alcohol abuse, and exercise. Since the endpoint of these trials is blood pressure, not mortality, the number of individuals involved—and therefore the costs—in such trials should be considerably lower than for other trials, e.g, the Hypertension Detection and Follow-up Program. Because high blood pressure is a major risk factor for the atherosclerotic diseases, its prevention and control by optimal means is a matter of the highest priority.

• **Recommendation**
Trials to test the primary prevention and control of high blood pressure by dietary change and exercise should be encouraged.

The National High Blood Pressure Control Effort

• **Conclusion**
In late 1972, the NHLBI launched the National High Blood Pressure Education Program in recognition of the fact that hypertension was an unsolved mass public health problem of large dimension. In the ensuing years, this Program played a key role in the broadly based national cooperative effort to detect millions of persons with hypertension in the United States, evaluate them medically, treat them, and bring their blood pressures under control. The percentage of hypertensives detected, treated, and controlled has risen from a low of 10-15 percent in the early 1970's to about 50 percent by the close of the decade. However, as is evident from this figure, much remains to be done. The challenge is particularly urgent because the Hypertension Detection and Follow-up Program has shown that antihypertensive treatment reduces mortality for persons with mild hypertension.

• **Recommendation**
NHLBI should expand its efforts to stimulate timely and effective detection, evaluation, and treatment of persons with high blood pressure. Based on the considerable achievements since its inception in 1973, the National High Blood Pressure Education Program should be expanded to realize its full potential for helping the Nation bring the massive hypertension problem fully under control.

Support for Preventive and Therapeutic Trials

• **Conclusion**
A major achievement of NHLBI in the 1970's was the successful conduct of a series of trials on the prevention of coronary heart disease and other atherosclerotic diseases, e.g., the Hypertension Detection and Follow-up Program, the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Coronary Primary Prevention Trial, the Beta-Blocker Heart Attack Trial, the Coronary Artery Surgery Study. One of these, the Hypertension Detection and

Follow-up Program, has completed its work. Its results are of great value in the effort to prevent atherosclerotic diseases. Other studies, still in progress, warrant the financial support necessary to bring them to successful completion.

- **Recommendation**

Support should be continued (and, where needed to assure optimal achievement, increased and extended) for the ongoing trials on the prevention of the atherosclerotic diseases.

Behavior Modification

- **Conclusion**

Optimal treatment of cardiovascular diseases frequently involves combined medical, surgical, pharmacological, and psychosocial approaches. Clinical experience suggests that behavioral factors are involved in all of these approaches, designed to influence lifestyles, cardiovascular risk factors, adherence to medical regimens, and outcomes of treatment. Psychosocial and behavioral characteristics before and during active intervention need to be assessed with respect to modifying behavior for both primary and secondary prevention of the atherosclerotic diseases.

- **Recommendation**

Controlled clinical trials should be supported to test the effectiveness of medical and behavioral procedures to modify ill-advised behavior, such as cigarette smoking, overeating, excessive drinking, physical inactivity, coronary-prone behavior, depression, and failure to comply with prescribed medical treatments.

Weight Control

- **Conclusion**

Behavioral approaches to weight control have generated several techniques for achieving short-term weight reduction. However, satisfactory methods for maintaining weight reduction in high proportions of obese persons over long periods of time have not yet been developed.

Moreover, the behavioral, physiological, and biochemical characteristics responsible for excessive caloric intake are not yet known.

- **Recommendation**

Research is needed to characterize the behaviors that create and maintain caloric imbalance, to determine the psychological and physiological effects of obesity, and to clarify its deleterious effects on the cardiovascular system. In addition, research is needed to develop behavioral approaches to the long-term maintenance of optimal weight.

Diabetes and Atherosclerosis

- **Conclusion**

For millions of people with clinical diabetes mellitus, particularly the common adult-onset type, atherosclerotic disease is the major cause of sickness, disability, and death. Atherosclerosis in people with diabetes does not differ qualitatively from atherosclerosis in nondiabetic persons, but is more severe and occurs earlier in life. Therefore, measures for the primary prevention of atherosclerotic disease and its complications recommended for the population in general and for high-risk people in particular have special relevance for the diabetic person. A major unsolved problem is whether long-term treatment with antihyperglycemic drugs will prevent or retard the manifestations of atherosclerotic disease in the diabetic.

- **Recommendation**

The NHLBI should encourage additional research and further population studies of diabetes and its cardiovascular complications. One important study would be to assess whether the use of antihyperglycemic drugs in adults with noninsulin-dependent diabetes improves prognosis with respect to atherosclerotic complications.

Systolic High Blood Pressure in the Elderly

- **Conclusion**

Large numbers of aging and elderly Americans have high systolic blood pressure without elevated diastolic pressure. Prospective epidemiologic studies have shown that individuals with isolated systolic hypertension are at increased risk of developing atherosclerotic disease and of dying from its complications. However, no information is available concerning the safety of controlling systolic hypertension by pharmacologic means or on the efficacy of such treatment for preventing atherosclerotic disease and death.

- **Recommendation**

Controlled trials on the long-term efficacy of pharmacologic treatment of systolic hypertension in elderly people should be expanded.

Alternatives to the Randomized Controlled Trial

- **Conclusion**

Randomized controlled trials are very difficult or impossible to use in the evaluation of some important problems in atherosclerosis. There is a need to develop other methods for evaluating interventions.

- **Recommendation**

For problems that are not amenable to investigation using controlled clinical trials, alternative methods should be examined. Among these alternatives are surveillance methods in the community, evaluating the benefit and risk of treatment regimens and of interventions designed to prevent and control atherosclerotic disease and its complications.

Transfer of Knowledge into Practical Use

• **Conclusion**
After successful completion of controlled clinical trials on the prevention and control of atherosclerotic disease and its complications, issues often remain to be resolved. Among these are problems of low-order toxicity, late toxicity, differential effects in different groups, or changes over time in benefit-to-risk ratio. Positive findings should lead to timely and effective implementation in the community at large. On the other hand, a negative result, as in the Coronary Drug Project, must be widely disseminated to avoid further use of ineffective or even harmful agents. These challenges in technology transfer have not been systematically and effectively addressed.

• **Recommendation**
The NHLBI should develop systems of surveillance to monitor the impact and consequences of technology transfer in the community.

Timely Application of Knowledge

• **Conclusion**
The NHLBI has a special responsibility to assure that research which is relevant to cardiovascular health be applied in an appropriate and timely manner. In undertaking this responsibility to translate new developments into practical benefits, NHLBI must assess expected benefits, hazards, and costs.

• **Recommendation**
The NHLBI should prepare and maintain an up-to-date catalogue of major diagnostic and therapeutic procedures employed for cardiovascular iliness, and encourage the development of information systems in medical care institutions to facilitate the monitoring and ongoing evaluation of diagnostic and therapeutic techniques.

Community Prevention Projects

• **Conclusion**
More information is needed concerning the effects of programs to achieve lifestyle change and risk factor reduction in communities through multiple forms and types of interventions. This information is necessary to effectively implement a strategy of primary prevention of the atherosclerotic diseases.

• **Recommendation**
The NHLBI should continue to support community-based prevention projects.

Reducing Dietary Fats and Cholesterol—National Cardiovascular Nutrition Education Program

• **Conclusion**
Epidemiologic evidence of an association between a high level of cholesterol in the serum and atherosclerosis is strong; saturated fats and cholesterol in the diet are major causes of this high level of cholesterol in the serum. Furthermore, extensive data from laboratory research, animal experimentation, and post mortem observations are consistent with the epidemiological evidence, although, unfortunately, gaps remain in knowledge of fundamental mechanisms.

During the 1970's, millions of American families modified their eating habits for health reasons. The change consisted of a moderate decrease in the intake of dietary cholesterol and saturated fat, and a moderate increase in the intake of unsaturated and polyunsaturated fat. Concomitantly, mean serum cholesterol levels decreased.

• **Recommendation**
The NHLBI should continue to pursue its policy of advising the health professions and the American public that future cardiovascular health status is likely to be improved by reducing the intake of dietary saturated fats and cholesterol, and preventing and controlling obesity. The advice should make clear that the evidence supporting such a recommendation is strong, but incomplete, that research on the issue must continue, and that the recommendation will be refined or modified as new knowledge indicates. To aid in the further development of its educational work in this area, NHLBI should consider undertaking, with other agencies, a National Cardiovascular Nutrition Education Program, modeled on the National High Blood Pressure Education Program.

National No-Smoking Education Program

• **Conclusion**
Cigarette smoking is one of the established major risk factors for coronary heart disease and the other atherosclerotic diseases. This fact is now widely appreciated, not only by health professionals but also by millions of Americans, and as a consequence millions have stopped smoking, particularly since the publication in 1964 of the *Report to the Surgeon General on Smoking and Health.* Although the number of smokers in the United States has decreased, in absolute terms the number is still large. Moreover, the proportion of heavy smokers in the population (25 + cigarettes per day) has not decreased and the proportion of teenage boys and girls who smoke regularly increased at least until the late 1970's. The combined use of cigarettes and the contraceptive pill by large numbers of women poses a special problem with respect to the risk of the atherosclerotic diseases.

• **Recommendation**
Using the National High Blood Pressure Education Program as a model, NHLB', in conjunction with other governmental health agencies concerned with smoking, should undertake a *National No-Smoking Education Program.* The program should be adequately funded to ensure effective impact in the mass media, and in the schools, workplaces, and communities of the Nation.

Biobehavioral Research

Biochemical and Physiological Concomitants of Behavior

• **Conclusion**
Basic neurobiologic studies have indicated mechanisms whereby behavioral processes influence metabolic and hemodynamic processes. Also, associations have been established indicating possible links between brain function, behavior, neuroendocrine and other physiological processes, and atherosclerotic cardiovascular disease. However, the mechanisms whereby psychosocial and behavioral processes influence atherosclerosis are still largely unknown.

• **Recommendation**
Research is needed on the physiological and biochemical links between behavioral processes and atherosclerosis. In particular, more research is needed on neurochemical, neuroendocrine, and metabolic functions which may influence atherosclerosis.

Social Basis of Health-Influencing Lifestyles

• **Conclusion**
The association between close interpersonal ties and a relative reduction in incidence and prevalence of atherosclerotic cardiovascular disease has been suggested in several epidemiologic studies involving several different behavioral measures in several different populations. However, the mechanisms of this possible protective effect are unknown.

• **Recommendation**
Research is needed to examine interrelationships among a range of behavioral factors—including social networks—and their influence on such socially determined factors as eating, drinking, and smoking habits; psychological factors such as levels of self-esteem and coping styles; and physiological factors such as circulating levels of catecholamines, secretion of cortisone, and other neuroendocrine substances.

Development of Health-Damaging Behaviors

• **Conclusion**
A great deal of information is available concerning human behavior under a variety of conditions. Procedures for psychosocial, cultural, and behavioral assessment are available and the technology for behavioral modification is well-developed. However, most experience in human behavior has been obtained with individuals displaying abnormal behavior patterns or with young normal adults under laboratory conditions. More information is needed about the natural history of the development of risk-related behavior patterns under free-living conditions, particularly during adolescence.

• **Recommendation**
Research is needed to develop standardized procedures for assessing the development of high-risk behaviors related to atherosclerotic cardiovascular disease. In particular, attention should be directed to factors that tend to decrease the long-term fixation of health damaging behaviors.

Collaboration with Clinical Scientists

• **Conclusion**
Several research programs have demonstrated the importance of biobehavioral factors in atherosclerotic cardiovascular disease. In particular, principles of behavioral science enter into clinical studies involving patient recruitment, assessment, education, management, followup, and final evaluation. However, standardization of behavioral procedures in human research is needed to increase their utility in assessment and management.

• **Recommendation**
Applications of behavioral science should be considered in many human research programs. Where appropriate, collaborations among biomedical and behavioral scientists should be established at all stages of research—from study design through study implementation to final evaluation.

Health Research Personnel

Decline in Training Support

• **Conclusion**
Support for physician trainees in cardiovascular research has lagged seriously behind that provided for physicians embarked on alternate pathways. This inadequate support has begun to compromise the national endeavor in research on atherosclerosis.

• **Recommendation**
Provision of competitive training stipends for physicians that will encourage them to engage in research on the basic, clinical, and preventive aspects of atherosclerosis should be implemented promptly.

Investigators Engaged in Atherosclerosis Research

• **Conclusion**
To sustain the current rate of progress in research and to undertake those research activities recently prescribed by the Congress, additional specialized investigators are needed.

• **Recommendation**
More scientists should be recruited in the following categories:

- Biochemists for studies of lipid and lipoprotein metabolism, the metabolism of the arterial wall, and the problems of vascular and cardiac transplantation;
- Laboratory investigators for studies of tissue metabolism and regional blood control during oxygen deficiency and impaired circulation of the brain, heart, and limbs;
- Clinical scientists (physicians) in all fields, with emphasis in the cerebrovascular and peripheral vascular diseases;
- Geneticists for studies of the genetic substrate of atherosclerosis;
- Epidemiologists and biostatisticians for research surveys and clinical trials in the cardiovascular area. Biostatisticians are particularly needed to assist other investigators in experimental design and analysis of their data. There is a special need for epidemiologists with cardiovascular specialization;
- Behavioral scientists to study social, psychological, and behavioral mechanisms influencing the basic process of atherosclerosis, behavioral procedures for clinical treatment and rehabilitation, and social influences important in preventing atherosclerotic cardiovascular diseases;
- Pathologists with an interest in the pathogenesis of atherosclerosis in man and experimental models;
- Biomedical engineering specialists with expertise in cardiovascular pathophysiology to improve noninvasive diagnostic instrumentation;
- Investigators with specialized training in endocrinology and metabolism as they relate to the complex relationships among diabetes, hormones, and cardiovascular diseases;
- Pediatricians knowledgeable in nutrition and in growth and development to study the origin of the adult risk factors as they occur in children, and the relationship of these characteristics in children to those in adults;
- Hematologists with special commitment to studying the relationship of thrombus formation to atherosclerosis in heart disease, stroke, and peripheral vascular disease; and
- Specialists in translating and disseminating information to practicing physicians and the American public, with the aim of improving health care and preventing disease.

Attracting Physicians to Atherosclerosis Research

• **Conclusion**
In recent years, the entry of physicians into clinical investigation, especially in the cardiovascular field, has decreased. This decrease poses a serious threat to the future of medical research in the United States because other types of scientists lack the physician's orientation to understanding and managing human disease. One important factor contributing to this decline is the training of the physician, which currently provides for a research experience only in blocks of time between medical school and fellowship that virtually dissociates the research exposure from education in the basic sciences and in clinical medicine. Another factor is the lack of adequate and secure salary support.

• **Recommendation**
Attention should be given to the kinds of training opportunities available, and to the adequacy and security of salary support:

- New types of training opportunities in research should be created by the National Institutes of Health for medical students and residents. By these devices, medical schools should be encouraged to weave research experiences into the curriculum so that the student can participate in research that is being conducted by established medical scientists. In determining the feasibility and formulation of such programs, the Director of NHLBI should consult representatives of medical education, medical research, and clinical specialty certification boards.
- Qualifying boards in the clinical specialties, including internal medicine, should be invited to develop one or more tracks that would enable potential clinical investigators to participate in clinical research in the course of residency training.
- The potential clinical investigator must be assured that secure and adequate salary is forthcoming. This salary support must encompass the period beyond fellowship training up to the achievement of academic tenure. It is strongly recommended that a mechanism be established to study approaches to this goal, and to ensure effective implementation.

Training More Cardiovascular Epidemiologists

• **Conclusion**
Important community research projects and community demonstrations (including public and professional education, as touched upon in the following conclusion) have gone undone or been unduly delayed because of the scarcity of physicians with a community (epidemiologic) perspective. The shortage is particularly acute with respect to those with a cardiovascular specialization.

• **Recommendation**
NHLBI should support the training of more cardiovascular epidemiologists. To assure that the specific needs in arteriosclerosis research are served, the NHLBI should:

- Provide program enrichment support for institutions with degree programs in epidemiology, to assure appropriate representation of cardiovascular disease in the curricula;
- Provide competitive traineeship support for individual students who pursue programs emphasizing research in cardiovascular disease epidemiology;
- Provide support for programs designed to orient cardiologists, internists, pediatricians, and other clinical specialists and research scientists to the special demands and capabilities of epidemiological research; and
- Provide continuing and expanded support for the current preventive cardiology teaching program of the NHLBI.

Personnel for Professional and Public Education

• **Conclusion**
Special talent, both doctoral and subdoctoral, is required for the design and implementation of effective health education projects aimed at improving health practices and enhancing healthy lifestyles for Americans. The need for such personnel in the future has not been addressed in a comprehensive way.

• **Recommendation**
The NHLBI should asses the personnel implications of the prevention-oriented education programs, both present and planned, and take steps to assure that the needs are met.

Need for Young Investigators in Behavioral Research

• **Conclusion**
Interdisciplinary research depends upon training young investigators to expand the scope of inquiry beyond their primary discipline. Because of the need for scientists with experience in biobehavioral research, programs have been set up for training scientists in the psychological and behavioral aspects of atherosclerosis. Professional development and training also has been enhanced by interdisciplinary workshops, conferences, and colloquia sponsored by the National Heart, Lung, and Blood Institute.

• **Recommendation**
Training programs in biobehavioral research should be expanded to include preventive cardiology with strong biobehavioral components. In addition, training programs in cardiology should be strongly encouraged to develop a biobehavioral component. Also, the National Heart, Lung, and Blood Institute should continue to sponsor interdisciplinary workshops, conferences, and colloquia in an effort to enhance the utilization of behavioral science in research on atherosclerosis.

Appendix A

Magnitude of the Problem of Atherosclerosis-Related Diseases

1. Coronary Heart Disease

The United States continues to experience one of the highest coronary death rates among middle-aged men in the world (Figures 9 and 10). Coronary heart disease is responsible each year for approximately 640,000 deaths (Table 5). It has been the leading cause of death for at least 40 years (Figure 11). This disease is not only a major problem among the elderly; it also causes premature death: about 140,000 people under the age of 65 died from it in 1978, and about 300,000 people under age 75. Moreover, as many as 400,000 coronary deaths occur suddenly and unexpectedly, before medical care and hospitalization are possible.

The bright spot in this grim picture is the recent decline in the death rate from coronary heart disease (Figures 2, 9-11). The trend of coronary mortality rates had been one of increase in the 1940's and 1950's; the trend reversed in the 1960's. The downward slope is steep and the reduction in number of premature deaths that it represents exceeds that for any other cause of death. In 1978 alone, 114,000 fewer deaths occurred among people age 35-74 than would have been expected had the rate not declined from its high level in 1968. These people, 50,000 of them under age 65, had their lives extended beyond 1978. As a direct result of the decline, average life expectancy has improved.

Many European nations are still experiencing a rising death rate for coronary heart disease; in others, which have shared in the reversal, the downward trend for middle-aged men has not matched that for this Nation (Figures 9 and 10). What caused the reversal and decline is not readily determined. Whether the decline

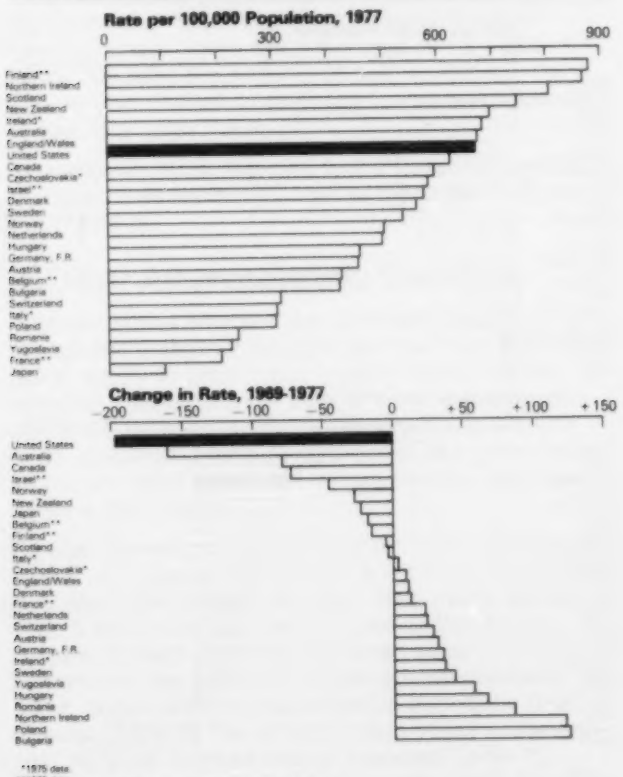


Figure 9.
Death Rates for Coronary Heart Disease by Country: Men 35-74 Years of Age

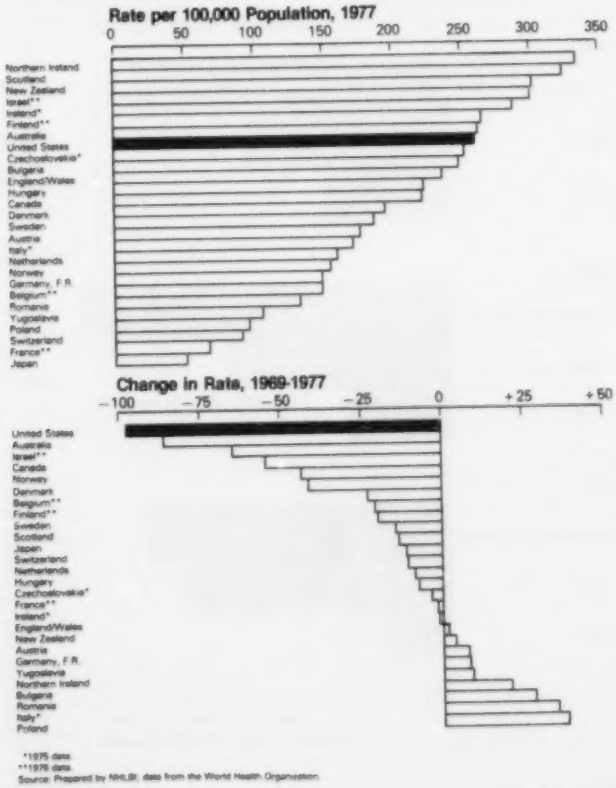


Figure 10.
Death Rates for Coronary Heart Disease by Country: Women 35-74 Years of Age

represents a decrease in incidence of coronary heart disease, a decrease in the fatality rate after heart attacks (case-fatality rate), or some combination of the two is still unsolved. A constellation of changes has been occurring in cigarette smoking, diet, exercise, serum cholesterol, and control of high blood pressure and it is a reasonable judgment that these have contributed to the decline.

Despite this favorable turn in mortality, the total number of deaths per year and the amount of illness and disability that the atherosclerotic diseases produce are monumental. In 1975, coronary heart disease was listed as the major reason for hospitalization for some 1,800,000 patients, accounting for 20 million hospital days (Tables 6 and 7). A national household survey in 1978 indicated that coronary heart disease affected about 4 million persons. Of these, over 2 million suffered some disability (Table 8), making coronary heart disease the second most common cause of chronic limitation of activity. Half of the people affected were under 65 years of age (Table 8). Finally, coronary heart disease is the leading basis for disability benefits among workers under Social Security. Among chronic diseases, it is the second leading cause of days confined to bed (Table 7).

Corresponding to the mortality, morbidity, and disability caused by coronary heart disease, the economic impact of the disease is great: $39 billion in a single year (1977) (Table 3). One of the reasons that the figure is so high is that large numbers of deaths from this disease occur during the productive years of life.

2. Cerebrovascular Diseases

As a general guide, about 70-80 percent of the mortality, morbidity, and economic impact of this group of diseases is estimated to represent the consequences of atherosclerosis. Cerebrovascular diseases caused 176,000 deaths in 1978. They constituted the third leading cause of death for middle-aged people, even though the great majority of deaths from cerebrovascular disease occurs in elderly people (Table 5). Fortunately, mortality from the cerebrovascular diseases has been decreasing for more than 40 years, and, since the early 1970's, the rate of decline has accelerated dramatically (Figure 2). In this regard, the United States has fared better than most other nations, particularly with respect to middle-aged persons (Figures 12 and 13).

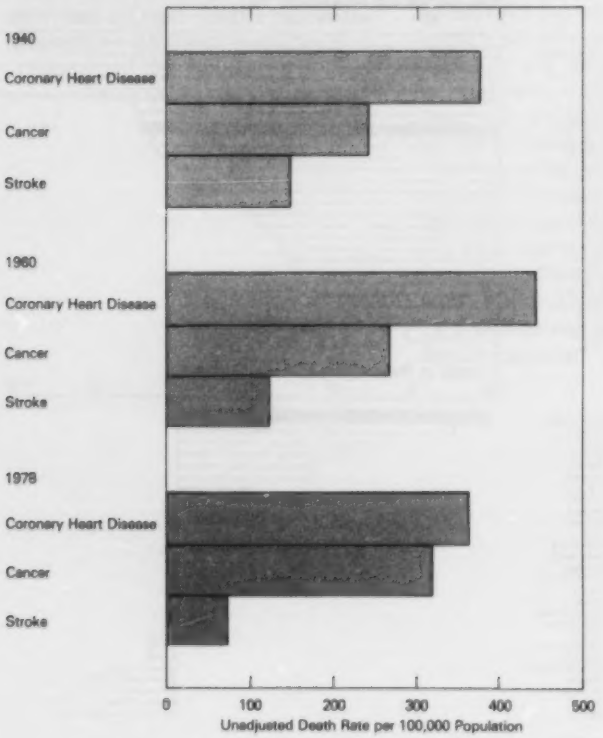
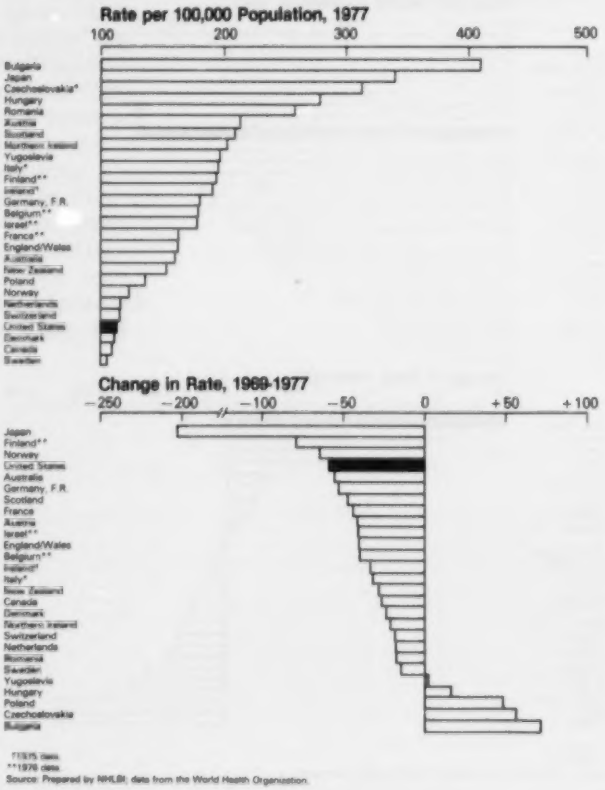


Figure 11.
Mortality Rates for Three Leading Causes of Death; Ages 35-74, United States; 1940, 1960, 1978



*1975 data.
**1978 data.
Source: Prepared by NHLBI; data from the World Health Organization.

Figure 12.
Death Rates for Cerebrovascular Diseases by Country: Men 35-74 Years of Age

Table 5. Number of Deaths from All Causes and from the Atherosclerotic Diseases, United States, 1978

Cause	Total	Under Age 65	Age 65 & over	Ages 35-74
All Causes	1,928,000	653,000	1,275,000	944,674
All Atherosclerotic Diseases*	873,000	174,000	699,000	380,666
Coronary Heart Disease	642,000	141,000	501,000	302,313
Cerebrovascular Diseases**	176,000	26,000	150,000	60,444
Other Atherosclerotic Diseases	55,000	7,000	48,000	17,909

Source: Prepared by the National Heart, Lung, and Blood Institute; data from the National Center for Health Statistics.

*See glossary for a definition of atherosclerotic disease. Detailed statistics concerning mortality, mortality trends, morbidity, and economic costs appear in Volume II of this report.
**Most (70-80 percent) of cerebrovascular disease deaths are due to atherosclerosis and its complications.

Although morbidity due to stroke is declining, the number of cases still remains impressively high. About 500,000 patients suffer strokes each year; of these, 400,000 are hospitalized. In 1978, a national household survey disclosed that 1.7 million persons were affected by cerebrovascular diseases; another approximately 100,000 afflicted persons reside in nursing homes (Table 8). Of the total of 1.8 million, nearly 700,000 were capable of only limited activity. The number of days of disability from these diseases is also very large (Table 7).

In economic terms, the cost to the Nation of cerebrovascular diseases in 1977 was of the order of $8 billion (Table 3).

3. Other Atherosclerotic Diseases

Atherosclerosis affects many different arteries, although not uniformly; besides the heart and brain, the blood supply to other major organs and to the extremities, particularly the legs, may be seriously compromised. Diabetic individuals are particularly prone to an accelerated form of atherosclerosis of the lower limbs, and there are over 4 million persons with diabetes in this Nation.

Precise data about this category of "other arterial diseases" are sparse, but enough is known to show that they also pose a major problem. They cause 55,000 deaths each year, and are now one of the leading causes of death (Table 5). Moreover, about 1 million persons are the victims of "other arterial diseases"; of these, about one-third are limited in activity by their disease (Table 6). The 5 million days spent in the hospital because of these arterial diseases (Table 7), while less than 2 percent of all hospital days, equal those for all infectious and parasitic diseases combined. Because so many residents in nursing homes are afflicted with occlusive arterial disease (Table 8), national health expenditures for this group of diseases amount to over $3 billion per year (Table 3).

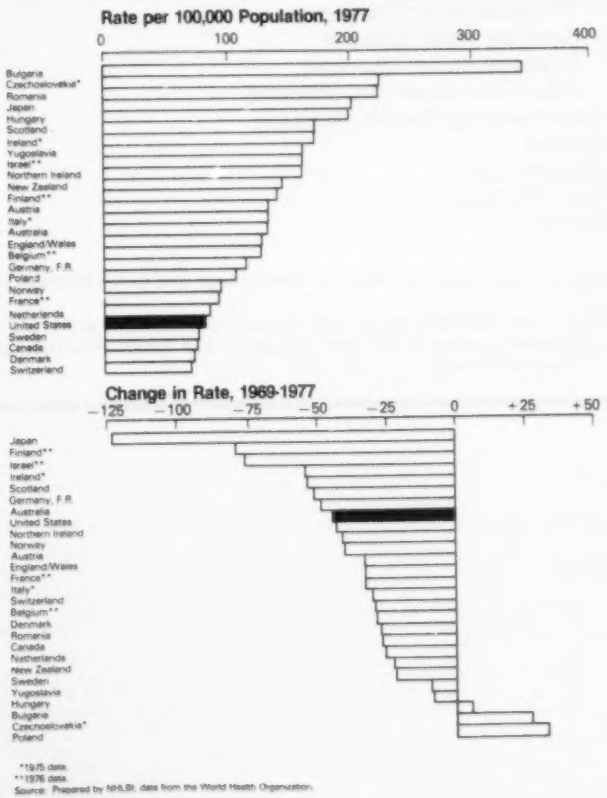


Figure 13.
Death Rates for Cerebrovascular Diseases by Country: Women 35-74 Years of Age

Table 6. Number of Inpatient Discharges for the Atherosclerotic Diseases, United States, 1975

Diagnosis	Total	Under Age 65	Age 65 & over
All Atherosclerotic Diseases	2,757,000	1,159,000	1,598,000
Coronary Heart Disease	1,832,000	858,000	974,000
Cerebrovascular Diseases	608,000	178,000	430,000
Other Atherosclerotic Diseases	317,000	123,000	194,000

Source: Prepared by the National Heart, Lung, and Blood Institute; data from the National Center for Health Statistics.

Table 7. Disability Days Attributed to the Atherosclerotic Diseases and Other Major Chronic Diseases, United States*

Disease	Hospital Days	Bed Days	Work-Loss Days	Restricted Activity Days
All Atherosclerotic Diseases	33	86	21	241
Coronary Heart Disease	20	61	18	184
Cerebrovascular Diseases	8	21	3	47
Other Atherosclerotic Diseases	5	4	**	10
Other Leading Chronic Diseases				
Arthritis	5	95	19	404
Hypertension	2	58	12	235
Back Problems	**	34	11	127
Cancer	22	***	***	***

Source: Prepared by the National Heart, Lung, and Blood Institute; data from the National Center for Health Statistics.

*All data in this table are for 1978, except hospital days, which are for 1977. Categories of disability days are not mutually exclusive.
**A numerical value is not cited because it was too small to meet standards of reliability or precision.
***Data unavailable.

Table 8. Prevalence of Atherosclerotic Disease and of Limitations Produced By It According to Age Groups, United States, 1978

Disease	Prevalence			Persons with Limitation of Activity	
	All Ages	Under Age 65	Age 65 and Over	Percent of Total	Number
All Atherosclerotic Diseases	6,761,400	2,844,000	3,917,400	51.3	3,468,000
Coronary Heart Disease	3,951,500	1,997,000	1,954,000	58.6	2,317,500
Not in Nursing Homes	3,929,000	1,997,000	1,932,000	58.4	2,295,000
In Nursing Homes	22,500	*	22,500	100.0	22,500
Cerebrovascular Diseases	1,817,500	691,000	1,126,500	43.9	797,500
Not in Nursing Homes	1,714,00	691,000	1,023,000	40.5	694,000
In Nursing Homes	103,500	*	103,500	100.0	103,500
Other Atherosclerotic Diseases	992,400	156,000	836,400	35.6	353,400
Not in Nursing Homes	728,000	156,000	572,000	12.2	89,000
In Nursing Homes	264,400	*	264,400	100.0	264,400

*Assumed that few are under age 65.

Source: Prepared by the National Heart, Lung, and Blood Institute; data from the National Center for Health Statistics.

Appendix B

Panels According to Dates, Topics, and Participants

Activities of Federal Agencies Related to the Atherosclerosis Problem

November 8, 1978

I. NHLBI Advisory Committees

Lipid Metabolism Advisory Committee –
Howard A. Eder, M.D.
Bruce Kottke, M.D.
Basil M. Rifkind, M.D.

Cardiology Advisory Committee –
Kay Millar, M.D.
Don H. Blount, Ph.D.

Arteriosclerosis and Hypertension Advisory Committee –
Mary Dempsey, Ph.D.
William R. Harlan, M.D.
Gardner McMillan, M.D.

Clinical Applications and Prevention Advisory Committee –
Robert E. Shank, M.D.
Manning Feinleib, M.D.
William J. Zukel, M.D.

Summary of Division of Heart and Vascular Diseases-Related Programs –
Mary Jane Jesse, M.D.

II. NHLBI Working Groups

Hypertension Task Force –
Joseph Wiener, M.D.

Task Force on Prevention and Treatment of Cardiovascular Disease in the Young –
Ronald Lauer, M.D.

National High Blood Pressure Education Program –
Graham Ward

Nutrition Education –
Steven Zifferblatt, Ph.D.

Task Force on Heart Disease Epidemiology –
Jeremiah Stamler, M.D.

Conference on the Decline in Coronary Heart Disease Mortality –
Sidney Blumenthal, M.D.

III. Other Federal Agencies

NHLBI Coordination –
Jay Moskowitz, Ph.D.

Office on Smoking and Health –
Robert Hutching

National Institute of Arthritis, Metabolism, and Digestive Diseases –
Lester E. Salans, M.D.

Center for Disease Control –
Gerald Cooper, M.D.

United States Department of Agriculture –
Kent K. Stewart, Ph.D.

Clinical Manifestations and Management of the Atherosclerotic Diseases

January 15, 1979

I. Noninvasive Techniques for Identifying Coronary Artery Disease

Overview –
Gerald M. Pohost, M.D.

Radionuclide Techniques to Evaluate Ventricular Function –
Robert H. Jones, M.D.

Echocardiographic Techniques –
Arthur E. Weyman, M.D.

Positron Emission Computerized Axial Tomography –
Heinrich R. Schelbert, M.D.

Myocardial Imaging by Gamma Radionuclide Techniques and Nuclear Magnetic Resonance Methods –
Gerald M. Pohost, M.D.
Eric T. Fossel, Ph.D.

Current Research in Nuclear Cardiology –
Henry N. Wagner, Jr., M.D.

II. Noninvasive Techniques for Identifying Cerebrovascular Disease and its Medical and Surgical Management

Overview –
James F. Toole, M.D.

Noninvasive Imaging of the Carotid Arteries Using B-Mode Ultrasound –
Charles P. Olinger, M.D.

Correlation of Coronary and Carotid Atherosclerosis –
John Moossy, M.D.

Medical Management of the TIA Patient –
J. P. Mohr, M.D.

Canadian Cooperative Study on Antiplatelet Aggregants and the Role of Antiplatelet Medications in the Future –
H. J. M. Barnett, M.D.

Surgical Management of Asymptomatic Patients with Carotid Bifurcation Bruits –
Jesse E. Thompson, M.D.

Extracranial Vascular Disease and Noninvasive Imaging Techniques as Seen from the Surgical Point of View –
Robert W. Barnes, M.D.

Intracranial Atherosclerosis and its Management –
John M. Tew, M.D.

Nature of the Atherosclerotic Process

February 26, 1979

I. Endothelium

E. J. Walter Bowie, M.D.

II. Prostaglandins

Salvador Moncada, M.D., Ph.D.

III. Connective Tissue Metabolism

Paul Bornstein, M.D.

IV. Cell Proliferation

Wilbur A. Thomas, M.D.

V. Blood Cells and Thrombosis

Philip W. Majerus, M.D.
Laurence A. Harker, M.D.

VI. Arterial Cell Response to Injury

Richard Minick, M.D.
Harvey Wolinsky, M.D.

Medical and Surgical Management of Coronary Artery Disease

March 5, 1979

I. Stable Angina

Medical Therapy –
Richard Gorlin, M.D.

Surgical Therapy –
Frank C. Spencer, M.D.

Percutaneous Transluminal Coronary Angioplasty –
Michael B. Mock, M.D.

Discussants –
Timothy Takaro, M.D.
John W. Kirklin, M.D.

II. Unstable Angina

Medical Therapy –
C. Richard Conti, M.D.

Surgical Therapy –
Lawrence Cohn, M.D.

Discussants –
Adolph M. Hutter, Jr., M.D.
Andrew S. Wechsler, M.D.

III. Variant Angina

Attilio Maseri, M.D.

IV. Myocardial Infarction

Medical Therapy –
Burton E. Sobel, M.D.

Surgical Therapy –
Mortimer J. Buckley, M.D.

Discussants –
Charles Rackley, M.D.
Andrew S. Wechsler, M.D.

V. Postmyocardial Infarction

Beta Adrenergic Blockade –
Sidney Goldstein, M.D.

Platelet Active Agents –
William T. Friedewald, M.D.

Sudden Cardiac Death

April 23, 1979

I. Who Is at Risk?

General Population –
Joseph T. Doyle, M.D.

Postmyocardial Infarction Population –
Arthur J. Moss, M.D.

Survivors of Cardiac Resuscitation –
Leonard A. Cobb, M.D.

II. Approaches for Identifying High-Risk Patients

William Ruberman, M.D.
Lawrence Hinkle, M.D.

III. Pathologic Studies in Sudden Cardiac Death

J. T. Lie, M.D.

IV. Mechanisms of Dysrhythmias

Experimental Models –
E. Neil Moore, D.V.M., Ph.D.

Role of the Autonomic Nervous System –
Matthew Levy, M.D.

Clinical and Experimental Mechanisms –
Robert Myerburg, M.D.

V. Approaches to Prevention of Sudden Cardiac Death

Emergency Systems and Education –
Richard S. Crampton, M.D.

Pharmacologic Approaches –
Benedict R. Lucchesi, M.D., Ph.D.

Clinical Considerations –
J. Thomas Bigger, Jr., Ph.D.

Ongoing Clinical Trials –
Curt D. Furberg, M.D.

Risk Factors and Underlying Pathophysiology

May 21, 1979

This program was developed and presented by Working Group members with the support of the following consultants:

Henry Blackburn, M.D.
Thomas B. Clarkson, D.V.M.
Scott M. Grundy, M.D., Ph.D.
Mary Jane Jesse, M.D.
Darwin Labarthe, M.D.
Gardner McMillan, M.D.
Edmond A. Murphy, M.D.
Adrian Ostfeld, M.D.
Ralph S. Paffenbarger, Jr., M.D.
Colin Schwartz, M.D.
Jack P. Strong, M.D.

I. Nutrition

II. Hypertension

III. Diabetes and Hyperglycemia

IV. Cigarette Smoking

V. Physical Activity

VI. Behavior and Psychosocial Factors

VII. Sex and Oral Contraceptives

VIII. Genetic Factors

IX. Childhood Precursors of Atherosclerosis

Decline in Mortality from the Atherosclerotic Diseases

June 4, 5, 1979

This program was developed and presented by Working Group members with support of the following consultants:

Graham Ward
Robert W. Wissler, M.D., Ph.D.
Steven Zifferblatt, Ph.D.

I. The Facts of the Decline

In Coronary Heart Disease Mortality

In Stroke Mortality

In Mortality for Other Atherosclerotic Diseases, All Major Cardiovascular Diseases, and All Causes

II. Impact on Coronary Heart Disease Mortality Rates of New Patterns of Treatment

Emergency Medical Services

Coronary Care Units

Rehabilitation

Long-term Care

Bypass Surgery

III. Impact of Lifestyle Changes

Smoking

Diet, Serum Cholesterol

Exercise

IV. Impact of Control of Hypertension

V. Multifactor Impact

VI. Recommendations of Earlier Working Groups and Task Forces

Intersociety Commission for Heart Disease Resources, 1970

Task Force on Arteriosclerosis, 1971

NHLBI Working Group on Epidemiology, 1979

NHLBI Conference on the Decline in CHD Mortality, 1979

VII. Research Programs on Prevention

NHLBI Trials of Primary Prevention

NHLBI Trials of Secondary Prevention

Community Demonstrations

Exercise and Stress Testing

July 16, 17, 1979

I. Stress Testing

For Latent CHD and Cardiac Reserve –
Robert A. Bruce, M.D.

Sensitivity and Specificity –
Stephen B. Epstein, M.D.

Myocardial Function and Perfusion –
Francis J. Klocke, M.D.

Effect of Training on Lipoprotein Profiles –
William L. Haskell, Ph.D.

Myocardial and Peripheral Biochemical Changes –
James Scheuer, M.D.

II. Exercise as Primary Prevention

Ralph S. Paffenbarger, Jr., M.D.

III. Exercise Rehabilitation after Myocardial Infarction

In-Hospital –
Nanette Wenger, M.D.

Early Post-MI –
Robert A. Bruce, M.D.

Post-Hospital –
Victor Froelicher, M.D.

Randomized Trials –
Albert Oberman, M.D.

IV. Considerations of Endpoints in the Use of Exercise

Albert Oberman, M.D.

V. Computer Approaches to Exercise Electrocardiography

Victor Froelicher, M.D.

Nature of the Atherosclerotic Process

August 27, 28, 1979

I. Endothelium

Endothelium and Atherogenesis –
Michael A. Gimbrone, Jr., M.D.

Injury, Repair, and Development in the Endothelium –
Stephen M. Schwartz, M.D., Ph.D.

Von Willebrand's Disease and Atherosclerosis –
David N. Fass, Ph.D.

Transport of Plasma Lipids Across Endothelial Membranes in Large Blood Vessels –
Eugene M. Renkin, Ph.D.

Endothelial "Rheology": Some Problems –
Donald L. Fry, M.D.

II. Platelets, the Vessel Wall, and Thrombosis

Platelets, the Vessel Wall, and Thrombosis –
Babette Weksler, M.D.

Thrombosis and Atherogenesis –
Philip W. Majerus, M.D.

III. Smooth Muscle and Cell-Lipoprotein Interactions

Vascular Smooth Muscle and Atherosclerosis –
Andrew P. Somlyo, M.D.

Risk Factors for Atherosclerosis –
Edwin L. Bierman, M.D.

Reversed Cholesterol Transport –
Yechezskiel Stein, M.D., Ph.D.
Olga Stein, M.D.

Lipoprotein-Cell Interaction: Research Areas Needing Greater Emphasis During the Next Five Years –
Daniel Steinberg, M.D., Ph.D.

Dietary Cholesterol and the Vascular Endothelium –
Christopher J. Fielding, Ph.D.

IV. Genetics and Atherosclerosis

Arno G. Motulsky, M.D.

Lipoproteins

September 24, 1979

I. Lipoproteins and Their Apoproteins

Relation to Atherosclerosis –
Robert Mahley, M.D., Ph.D.

Determinations –
Gustav Schonfeld, M.D.

Metabolism and Structure –
Bryan Brewer, M.D.

II. Role of the Liver in Lipoprotein Metabolism

John M. Dietschy, M.D.

III. Control of Lipoprotein Levels

Diet and Drugs –
Howard A. Eder, M.D.

Hormones and Physical Activity –
Ronald Krauss, M.D.

IV. Lipoprotein Levels and Metabolism

Pediatric and Adolescent –
Peter Kwiterovich, M.D.

Adult and Geriatric –
John A. Morrison, Ph.D.

Epidemiology

October 22, 1979

This program was developed and presented by Working Group members with the support of the following consultants:

E. H. Ahrens, Jr., M.D.
D. Mark Hegsted, M.D.
Richard Scheffler, Ph.D.
Henry W. Riecken, Ph.D.

I. Diet and Cardiovascular Health

Donald B. Zilversmit, Ph.D.

Discussants –
E. H. Ahrens, Jr., M.D.
D. Mark Hegsted, M.D.

II. Health Research Personnel

John B. Dunbar, D.M.D., Dr.P.H.

Discussants –
Richard Scheffler, Ph.D.
Henry W. Riecken, Ph.D.

III. Health Services Research

Reuel A. Stallones, M.D., M.P.H.

IV. Future Directions in Epidemiology

Jeremiah Stamler, M.D.

Behavior and Atherosclerosis

November 15, 1979

I. Biobehavioral Research Relating to Atherosclerosis

J. Alan Herd, M.D.

II. Pathogenesis of Atherosclerosis

Neurochemical Mechanisms –
Floyd E. Bloom, M.D.

Psychosocial Influences –
David C. Glass, Ph.D.

Sociocultural Risk Factors in Coronary Heart Disease –
S. Leonard Syme, Ph.D.

Coronary Heart Disease and Sudden Death –
Robert S. Eliot, M.D.

III. Diagnosis and Treatment

Principles of Behavior Analysis and Cardiovascular Risk Factors –
Joseph V. Brady, Ph.D.

Behavioral Processes and Treatment Outcomes in Coronary Heart Diseases –
Redford B. Williams, Jr., M.D.

IV. Rehabilitation

Postmyocardial Infarction –
L. Howard Hartley, M.D.

V. Prevention of Atherosclerosis

Developmental Approaches to Risk Factors -
Richard I. Evans, Ph.D.

Community Approaches to Risk Factor Reduction -

European Studies:
Pekka Puska, M.D.

American Studies:
John W. Farquhar, M.D.

VI. Resources, Manpower, and Training Programs

Joseph D. Matarazzo, Ph.D.

VII. Summary

J. Alan Herd, M.D.

Peripheral Vascular Disease, Cardiac Transplantation, and Diabetes

December 10, 1979

I. Peripheral Vascular Disease

John A. Spittell, Jr., M.D.

II. Cardiac Transplantation

Richard R. Lower, M.D.

III. Report of National Conference on Diabetes: Current Status and Future Directions

Cardiovascular Disease -
M. Bernadette Garvey, M.D.

Obesity -
Sidney Blumenthal, M.D.

IV. Decline in Mortality

Reuel A. Stallones, M.D., M.P.H.

Appendix C

Participants in the Panel Discussions

E. H. Ahrens, Jr., M.D.
Professor
Rockefeller University
New York, New York

Robert W. Barnes, M.D.
Professor of Surgery
Medical College of Virginia
Richmond, Virginia

H. J. M. Barnett, M.D.
Professor and Chairman
Department of Clinical Neurological Sciences
University of Western Ontario
London, Ontario, Canada

Edwin L. Bierman, M.D.
Head, Division of Endocrinology and Metabolism
Department of Medicine
University of Washington
Seattle, Washington

J. Thomas Bigger, Jr., Ph.D.
Professor of Medicine and Pharmacology
Presbyterian Hospital
New York, New York

Henry Blackburn, M.D.
Laboratory of Physiological Hygiene
University of Minnesota
Minneapolis, Minnesota

Floyd E. Bloom, M.D.
The Salk Institute
San Diego, California

Don H. Blount, Ph.D.
Graduate Dean
Vice Provost for Research
University of Missouri, Columbia
Columbia, Missouri

Sidney Blumenthal, M.D.
Vice President
American Bureau for Medical Advancement in China
New York, New York
(Cochairman, Working Group on Arteriosclerosis)

Paul Bornstein, M.D.
Professor of Biochemistry and Medicine
Health Sciences
University of Washington School of Medicine
Seattle, Washington

E. J. Walter Bowie, M.D.
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

Joseph V. Brady, Ph.D.
Professor of Behavioral Biology
The Johns Hopkins University
Baltimore, Maryland

Bryan Brewer, M.D.
Chief, Molecular Disease Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Robert A. Bruce, M.D.
Professor of Medicine
Co-Director, Division of Cardiology
University of Washington
Seattle, Washington

Mortimer J. Buckley, M.D.
Chief, Cardiac Surgical Unit
Massachusetts General Hospital
Boston, Massachusetts

Thomas B. Clarkson, D.V.M.
Professor of Comparative Medicine
Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, North Carolina

Leonard A. Cobb, M.D.
Professor of Medicine
University of Washington
Harborview Medical Center
Seattle, Washington

Lawrence S. Cohen, M.D.*
Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

Lawrence Cohn, M.D.
Associate Professor of Surgery
Peter Bent Brigham Hospital
Harvard Medical School
Boston, Massachusetts

C. Richard Conti, M.D.
Chief, Division of Cardiology
J. Hillis Miller Health Center
University of Florida
Gainesville, Florida

Gerald Cooper, M.D.
Chief, Metabolic Chemistry Branch
Clinical Chemistry Division
Bureau of Laboratories
Center for Disease Control
Atlanta, Georgia

Richard S. Crampton, M.D.
Professor of Medicine
Director, Coronary Care System
University of Virginia Medical Center
Charlottesville, Virginia

*Indicates member of Working Group on Arteriosclerosis

Mary Dempsey, Ph.D.
Professor
Department of Biochemistry
University of Minnesota
Minneapolis, Minnesota

John M. Dietschy, M.D.
Department of Internal Medicine
University of Texas Health Science Center
Dallas, Texas

Joseph T. Doyle, M.D.
Professor of Medicine
Head, Division of Cardiology
Albany Medical College
Albany, New York

John B. Dunbar, D.M.D., Dr. P.H.*
Special Assistant
Office of the Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

George Eaves, Ph.D.
Assistant to the Director
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Howard A. Eder, M.D.
Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Robert S. Eliot, M.D.
Professor of Cardiovascular Medicine
University of Nebraska Medical Center
Omaha, Nebraska

Glen Elliott, Ph.D., M.D.
Visiting Fellow
Institute of Medicine
Washington, D.C.

Arnold Engel, M.D.
Medical Officer
Health Examinations Statistics
Hyattsville, Maryland

Stephen B. Epstein, M.D.
Chief, Cardiology Branch
Division of Intramural Research
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Richard I. Evans, Ph.D.
Professor of Psychology
University of Houston
Houston, Texas

John W. Farquhar, M.D.
Director, Stanford Heart Disease Prevention Program
Stanford University Medical School
Stanford, California

David N. Fass, Ph.D.
Assistant Professor of Medicine and Biochemistry
Department of Hematology Research
Mayo Medical School
Rochester, Minnesota

Manning Feinleib, M.D.
Associate Director
Epidemiology and Biometry Program
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Christopher J. Fielding, Ph.D.
Cardiovascular Research Institute
University of California Medical Center
San Francisco, California

Alfred P. Fishman, M.D.*
Director, Cardiovascular-Pulmonary Division
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
(Chairman, Working Group on Arteriosclerosis)

Eric T. Fossel, Ph.D.
Assistant Professor of Biophysics
Harvard Medical School
Boston, Massachusetts

William T. Friedewald, M.D.
Associate Director, Clinical Applications and
Prevention Program
Clinical Trials Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Victor Froelicher, M.D.
University Hospital
University of California
San Diego, California

Donald L. Fry, M.D.
Chief, Laboratory of Experimental Atherosclerosis
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Curt D. Furberg, M.D.
Medical Officer
Clinical Trials Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

M. Bernadette Garvey, M.D.*
Associate Professor
Department of Medicine
St. Michael's Hospital
Toronto, Ontario, Canada

Michael A. Gimbrone, Jr., M.D.
Department of Pathology
Peter Bent Brigham Hospital
Boston, Massachusetts

David C. Glass, Ph.D.
Professor of Psychology
Graduate School and University Center
City University of New York
New York, New York

Sidney Goldstein, M.D.
Head, Division of Cardiovascular Medicine
Henry Ford Hospital
Detroit, Michigan

Richard Gorlin, M.D.
Professor and Chairman, Department of Medicine
Mt. Sinai School of Medicine
New York, New York

Scott M. Grundy, M.D., Ph.D.
Chief, Metabolic Section
Veterans Administration Hospital
San Diego, California

Edgar Haber, M.D.*
Chief, Cardiac Unit
Massachusetts General Hospital
Boston, Massachusetts

David A. Hamburg, M.D.*
President
Institute of Medicine
Washington, D.C.

Laurence A. Harker, M.D.
Professor of Medicine
Department of Hematology
Harborview Medical Center
Seattle, Washington

William R. Harlan, M.D.
Professor and Chairman
Postgraduate Medicine and Health Professions Education
University of Michigan Medical School
Ann Arbor, Michigan

L. Howard Hartley, M.D.
Associate Professor of Medicine
Cardiac Unit
Massachusetts General Hospital
Boston, Massachusetts

William L. Haskell, Ph.D.
Clinical Assistant Professor of Medicine
Stanford Heart Disease Prevention Program
Stanford University
Palo Alto, California

D. Mark Hegsted, M.D.
Administrator, Human Nutrition Center
United States Department of Agriculture
Washington, D.C.

J. Alan Herd, M.D.
Associate Professor of Psychobiology
New England Regional Primate Research Center
Southborough, Massachusetts

Lawrence Hinkle, M.D.
Professor of Medicine
Cornell University Medical College
New York, New York

Robert Hutching
Associate Director for Information
Office on Smoking and Health
Rockville, Maryland

Adolph M. Hutter, Jr., M.D.
Associate Director
Coronary Care Unit
Massachusetts General Hospital
Boston, Massachusetts

Mary Jane Jesse, M.D.
Director, Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Robert H. Jones, M.D.
Associate Professor of Surgery
Assistant Professor of Radiology
Duke University Medical Center
Durham, North Carolina

John W. Kirklin, M.D.
Professor and Chairman
Department of Surgery
University of Alabama
School of Medicine and Medical Center
Birmingham, Alabama

Francis J. Klocke, M.D.
Professor of Medicine
State University of New York at Buffalo
Buffalo, New York

Bruce Kottke, M.D.
Head, Cardiovascular Research Unit
Mayo Clinic
Rochester, Minnesota

Ronald Krauss, M.D.
Donner Laboratory
University of California at Berkeley
Berkeley, California

Peter Kwiterovich, M.D.
Johns Hopkins University School of Medicine
Baltimore, Maryland

Darwin Labarthe, M.D., Ph.D.
Professor of Epidemiology
University of Texas School of Public Health
Houston, Texas

Ronald Lauer, M.D.
Professor of Pediatric Cardiology
University of Iowa Hospital and Clinic
Iowa City, Iowa

Robert I. Levy, M.D.
Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

*Indicates member of Working Group on Arteriosclerosis

Matthew Levy, M.D.
Chief, Investigative Medicine
Mt. Sinai Hospital
Cleveland, Ohio

J. T. Lie, M.D.
Professor of Pathology
Mayo Clinic and Mayo Medical School
Rochester, Minnesota

Richard R. Lower, M.D.
Chairman, Division of Thoracic Surgery
Medical College of Virginia
Richmond, Virginia

Benedict R. Lucchesi, M.D., Ph.D.
Professor of Pharmacology
University of Michigan
Ann Arbor, Michigan

Robert Mahley, M.D., Ph.D.
Gladstone Foundation Institute for Cardiovascular Disease
University of California
San Francisco General Hospital
San Francisco, California

Philip W. Majerus, M.D.
Professor of Medicine and Biochemistry
Division of Hematology-Oncology
Washington University School of Medicine
St. Louis, Missouri

Attilio Maseri, M.D.
Professor of Cardiovascular Medicine
Sir John Michael Chair of Cardiovascular Medicine
London, England

Joseph D. Matarazzo, Ph.D.
Professor of Medical Psychology
Health Sciences Center
University of Oregon
Portland, Oregon

Henry C. McGill, Jr., M.D.*
Professor, Department of Pathology
Graduate School of Biomedical Sciences
University of Texas Health Science Center
San Antonio, Texas

Gardner McMillan, M.D.
Director, Etiology of Arteriosclerosis and Hypertension Program
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Kay Millar, M.D.
Associate Professor of Medicine
Cardiology Division
University of Utah Medical Center
Salt Lake City, Utah

Richard Minick, M.D.
Professor, Department of Pathology
Cornell University Medical College
New York, New York

Michael B. Mock, M.D.
Chief, Cardiac Diseases Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

J. P. Mohr, M.D.
Professor and Chairman
Department of Neurology
University of South Alabama College of Medicine
Mobile, Alabama

Salvador Moncada, M.D., Ph.D.
Head, Department of Prostaglandin Research
The Wellcome Research Laboratories
Beckenham, Kent, England

E. Neil Moore, D.V.M., Ph.D.
Professor of Physiology in Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

John Moossy, M.D.
Professor of Pathology and Neurology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

John A. Morrison, Ph.D.
Lipid Research Center
University of Cincinnati College of Medicine
Cincinnati, Ohio

Jay Moskowitz, Ph.D.
Associate Director for Program Planning and Evaluation
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Arthur J. Moss, M.D.
Clinical Associate Professor of Medicine
University of Rochester School of Medicine
Rochester, New York

Arno G. Motulsky, M.D.
Professor of Medicine and Geriatrics
Director, Center for Inherited Diseases
University of Washington
Seattle, Washington

Edmond A. Murphy, M.D.
Moore Clinic
Johns Hopkins Hospital
Baltimore, Maryland

Robert Myerburg, M.D.
Professor of Medicine and Physiology
University of Miami School of Medicine
Miami, Florida

Alex Nichols, Ph.D.*
Professor of Medical Physics
Department of Biophysics and Medical Physics
University of California
Berkeley, California

Elena O. Nightingale, M.D., Ph.D.
Director, Division of Health Promotion and Disease Prevention
Institute of Medicine
Washington, D.C.

Albert Oberman, M.D.
Director, Division of Preventive Medicine
University of Alabama
Birmingham, Alabama

Charles P. Olinger, M.D.
Professor of Neurology
University of Cincinnati
Cincinnati, Ohio

Adrian Ostfeld, M.D.
Professor of Epidemiology
Yale University School of Medicine
New Haven, Connecticut

Barbara Packard, M.D., Ph.D.
Associate Director for Cardiology
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Ralph S. Paffenbarger, Jr., M.D.
State Department of Public Health
Berkeley, California

Gerard Piel
President and Publisher
Scientific American
New York, New York

Gerald M. Pohost, M.D.
Cardiac Unit
Massachusetts General Hospital
Boston, Massachusetts

M. Jeanne Pontious, R.N.*
Associate Professor of Nursing
Indiana University
Indianapolis, Indiana

Pekka Puska, M.D.
North Karelia Project
University of Kuopio
Kuopio, Finland

Charles Rackley, M.D.
Professor of Medicine
University of Alabama School of Medicine
Birmingham, Alabama

Eugene M. Renkin, Ph.D.
Chairman, Department of Human Physiology
University of California at Davis
Davis, California

Henry W. Riecken, Ph.D.
Professor of Behavioral Sciences
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Basil M. Rifkind, M.D.
Chief, Lipid Metabolism Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

John Ross, Jr., M.D.*
Professor of Medicine
Director, Cardiovascular Division
School of Medicine
University of California at San Diego
La Jolla, California

Russell Ross, Ph.D.*
Professor of Pathology
University of Washington School of Medicine
Seattle, Washington

William Ruberman, M.D.
Director of Medical Research
Health Insurance Plan of Greater New York
New York, New York

David C. Sabiston, Jr., M.D.*
Professor and Chairman
Department of Surgery
Duke University Medical Center
Durham, North Carolina

Lester B. Salans, M.D.
Associate Director for Diabetes, Endocrine and Metabolic Diseases
National Institute of Arthritis, Metabolism, and Digestive Diseases
National Institutes of Health
Bethesda, Maryland

Richard Scheffler, Ph.D.
Economics Department
George Washington University
Washington, D.C.

Heinrich R. Schelbert, M.D.
Associate Professor of Radiological Sciences
Division of Nuclear Medicine
University of California at Los Angeles
Los Angeles, California

James Scheuer, M.D.
Montefiore Hospital Center
Bronx, New York

Gustav Schonfeld, M.D.
Lipid Research Center
Washington University Medical Center
St. Louis, Missouri

Colin Schwartz, M.D.
Department of Pathology
University of Texas Health Science Center
San Antonio, Texas

Stephen M. Schwartz, M.D., Ph.D.
Assistant Professor
Department of Pathology
University of Washington
Seattle, Washington

*Indicates member of Working Group on Arteriosclerosis

Robert E. Shank, M.D.
Danforth Professor and Head, Department of Preventive Medicine
Washington University Medical School
St. Louis, Missouri

Burton E. Sobel, M.D.
Director, Cardiovascular Division
Barnes Hospital
Washington University School of Medicine
St. Louis, Missouri

Andrew P. Somlyo, M.D.
Director, Pennsylvania Muscle Institute
Presbyterian/University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Edward Sondik, Ph.D.
Chief, Program Analysis and Evaluation Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Frank C. Spencer, M.D.
Chairman, Department of Surgery
New York University Medical Center
New York, New York

John A. Spittell, Jr., M.D.
Professor of Medicine
Consultant, Cardiovascular Diseases
Mayo Clinic
Rochester, Minnesota

Reuel A. Stallones, M.D., M.P.H.*
Dean, School of Public Health
The University of Texas
Houston, Texas

Jeremiah Stamler, M.D.*
Professor and Chairman
Department of Community Health and Preventive Medicine
Northwestern University Medical School
Chicago, Illinois

Olga Stein, M.D.
c/o Dr. Russell Ross
University of Washington School of Medicine
Seattle, Washington

Yechezskiel Stein, M.D., Ph.D.
c/o Dr. Russell Ross
University of Washington School of Medicine
Seattle, Washington

Daniel Steinberg, M.D., Ph.D.
Professor of Medicine
Head, Division of Metabolic Diseases
Department of Medicine
University of California at San Diego
La Jolla, California

Kent K. Stewart, Ph.D.
Chief, Nutrient Composition Lab
Nutrition Institute
United States Department of Agriculture
Beltsville, Maryland

Jack P. Strong, M.D.
Professor and Chairman
Department of Pathology
Louisiana State University Medical Center
New Orleans, Louisiana

S. Leonard Syme, Ph.D.
Professor of Epidemiology
Department of Biomedical and Environmental Health Sciences
School of Public Health
University of California
Berkeley, California

Timothy Takaro, M.D.
Chief, Surgical Service
Veterans Administration Hospital
Asheville, North Carolina

John M. Tew, Jr., M.D.
Director, Section of Neurosurgery
Good Samaritan Hospital
Cincinnati, Ohio

Thomas Thom
Statistician
Biometrics Research Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Wilbur A. Thomas, M.D.
Chairman, Department of Pathology
Albany Medical College
Albany, New York

Jesse E. Thompson, M.D.
Attending Surgeon
Baylor University Medical Center
Dallas, Texas

James F. Toole, M.D.*
Professor and Chairman
Department of Neurology
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Henry N. Wagner, Jr., M.D.
Professor of Medicine, Radiology, and Environmental Health Sciences
Director, Division of Nuclear Medicine and Radiation Health
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Graham Ward
Chief, Health Education Branch
Office of Prevention, Education and Control
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

John Watson, Ph.D.
Chief, Devices and Technology Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Andrew S. Wechsler, M.D.
Associate Professor of Surgery
Assistant Professor of Physiology and Pharmacology
Duke University Medical Center
Durham, North Carolina

Stephen Weiss, Ph.D.
Chief, Behavioral Medicine Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Babette Weksler, M.D.
Department of Hematology/Oncology
Cornell University Medical College
New York, New York

Nanette Wenger, M.D.
Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Arthur E. Weyman, M.D.
Assistant Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Joseph Wiener, M.D.
Professor and Chairman
Department of Pathology
Wayne State University School of Medicine
Detroit, Michigan

Redford B. Williams, Jr., M.D.
Associate Professor of Psychiatry
Duke University Medical Center
Durham, North Carolina

Ronald Wilson
Division of Analysis
National Center for Health Statistics
Hyattsville, Maryland

Robert W. Wissler, M.D., Ph.D.
Professor and Chairman
Department of Pathology
University of Chicago
Chicago, Illinois

Harvey Wolinsky, M.D., Ph.D.
Professor, Departments of Medicine and Pathology
Albert Einstein College of Medicine
Bronx, New York

Steven Zifferblatt, Ph.D.
Special Assistant to the Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Donald B. Zilversmit, Ph.D.*
Professor of Nutritional Biochemistry
Division of Nutritional Sciences
Cornell University
Ithaca, New York

William J. Zukel, M.D.
Associate Director
Clinical Applications and Prevention
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

---

*Indicates member of Working Group on Arteriosclerosis

Appendix D

Other Acknowledgements

The Working Group on Arteriosclerosis is also indebted to the following individuals who provided expert advice about topics that related to their special fields of interest in arteriosclerosis.

Bonita Condon
Acting Chief
Information Systems Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Elizabeth Barrett-Conner, M.D.
Associate Professor
Department of Community Medicine
The University of California at San Diego
La Jolla, California

Arnold Engel, M.D.
Medical Officer
Health Examination Statistics
National Center for Health Statistics
Hyattsville, Maryland

Thomas Thom
Statistician
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

C. Morton Hawkins, Sc.D.
Professor of Biometry
School of Public Health
The University of Texas
Houston, Texas

Donald MacCanon, Ph.D.
Chief, Research Training and Development Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Elena Nightingale, M.D., Ph.D.
Director
Division of Health Promotion and Disease Prevention
Institute of Medicine
Washington, D.C.

W. McFate Smith, M.D.
Clinical Professor of Medicine
Chief, Research Coordination Branch
U.S. Public Health Service Hospital
University of California at San Francisco
San Francisco, California

Stephen Weiss, Ph.D.
Chief
Behavioral Medicine Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Appendix E

National Heart, Lung, and Blood Institute Support of Cardiovascular Research

Table 9. Distribution of Research Funds by National Plan Categories, Division of Heart and Vascular Diseases, NHLBI, Fiscal Year 1979

National Plan Categories	Training	Research	Contracts	Total
Arteriosclerosis	1,244,811	44,638,170	30,615,481	76,498,462
Hypertension	2,851,159	39,895,104	17,760,234	60,506,497
Cerebrovascular Diseases	541,164	4,089,407	1,751,314	6,381,885
Peripheral Vascular Disease	512,855	6,171,716	1,701,879	8,386,450
Coronary Heart Disease	2,729,515	47,314,991	10,363,575	60,408,081
Congenital Heart and Rheumatic Heart Disease	851,049	9,384,275	290,154	10,525,478
Cardiomyopathies and Infection	492,958	5,148,983	81,423	5,723,364
Arrhythmias	1,957,328	19,535,364	5,151,628	26,644,320
Heart Failure/Shock	2,010,555	18,544,577	236,275	20,791,407
Circulatory Assistance	50,650	7,357,297	10,435,438	17,843,385
Total	13,242,044	202,079,884	78,387,401	293,709,329

Source: National Heart, Lung, and Blood Institute

Appendix F

Glossary

Aneurysm
An abnormal dilation of the wall of an artery, often the aorta, due to weakening caused by either a congenital defect or by disease, e.g., atherosclerosis.

Angina Pectoris
A sudden and severe distinctive discomfort in the chest, often extending to the left arm and shoulder and associated with a sense of suffocation. It usually results from atherosclerotic narrowing of the arteries supplying the heart muscle (coronary arteries).

Angiography
An x-ray technique used to examine the interior of the heart and great blood vessels. It involves injecting intravenously a fluid opaque to x-rays and taking serial x-rays as the agent flows through consecutive vessels and cardiac chambers.

Anticoagulant
A medication which is administered to delay clotting of the blood. It is used to prevent new clots from forming, or existing clots from enlarging, but does not dissolve an existing clot.

Aorta
The great trunk of the arterial tree, which originates from the left ventricle of the heart and subdivides thereafter into branches for delivery of blood to the head and body.

Aortography
X-ray examination of the aorta and its main branches after injection of a radio-opaque dye (see Angiography).

Aphasia
Loss or impairment of the power to express oneself by speech, writing, or signs or to comprehend spoken or written language.

Arrhythmia
An irregularity or abnormality in rhythm of the heartbeat. Some arrhythmias are life-threatening because of excessively rapid or chaotic heart action.

Arteriosclerosis
A scientific term for "hardening of the arteries." It is a broad term that does not identify either the mechanism responsible for hardening of the arterial wall or the size of the affected arteries or the type of arterial hardening (see Atherosclerosis).

Artery
Two main sets of arteries exist in the body: those to the lung (pulmonary arteries) and those that deliver blood elsewhere in the body (systemic arteries). The systemic arteries are branches of the aorta and carry oxygenated blood. Atherosclerosis regularly affects systemic arteries and only rarely affects pulmonary arteries.

Atherogenesis
The chain of events leading to the development of atherosclerosis in the arterial wall.

Atherosclerosis
A form of arteriosclerosis affecting large and medium-sized arteries. The inner surface of the artery wall is thick and crusty because of accumulation of cells, fatty deposits, particularly cholesterol, and other tissues formed by the cells (see Arteriosclerosis).

Blood Pressure
A measure of the pressure exerted by the blood against the walls of the artery. Distinction is made between systolic and diastolic blood pressure. The systolic blood pressure is generated by contraction of the heart muscle; diastolic pressure occurs when the heart muscle relaxes between beats. Blood pressure is generally expressed in terms of both systolic and diastolic pressures, e.g. 120/80.

Cardiac
Pertaining to the heart.

Cardiovascular
Pertaining to the heart and blood vessels.

Cardiovascular-Renal
Pertaining to the heart, blood vessels, and kidneys.

Cerebral Vascular Accident
A medical synonym for a "stroke." A stroke results from a critical decrease in blood flow to some part of the brain. It is generally caused by one of four conditions:

1. a blood clot forming in an atherosclerotic artery supplying the brain (cerebral thrombosis)
2. a rupture of the wall of a cerebral artery (cerebral hemorrhage)
3. a piece of clot or other material from another part of the systemic arterial tree or the heart which flows to the brain and obstructs a cerebral vessel (cerebral embolism)
4. pressure on a blood vessel as by a tumor.

Cerebrovascular
The same as Cerebral Vascular. Pertaining to the blood vessels supplying the brain.

Cholesterol
A fat-like substance present in the blood, the brain, and all other tissues throughout the body, as well as in much of the food of animal origin that we eat. Cholesterol has been implicated in the development of atherosclerosis. In blood tests, the normal level for adult Americans age 30 and over is generally regarded as less than 220 milligrams per 100 ml. Higher values are associated with greater risk of premature atherosclerotic disease.

Circulatory
Pertaining to the heart, blood vessels, and the circulation of the blood.

Claudication
Pain and lameness or limping caused by defective circulation of the blood in the arteries of the limbs.

Closed Population
A study population composed of institutionalized individuals.

Coagulation
The process of clotting, which involves a change from a liquid state to a sludge or solid state.

Collateral Circulation
Arterial vessels which deliver blood to a compromised area after the main vessel has been occluded.

Congestive Heart Failure
Either or both ventricles can fail. Heart failure is identified by inability of the heart to eject normal quantities of blood at normal filling pressures. As a result of the high filling pressures of the heart and, in time, of the decrease in cardiac output, excessive quantities of fluid accumulate in the lungs and dependent parts of the body. Congestive heart failure represents a combination of disorders reflecting both the low cardiac output and the high pressures behind the ventricle (or ventricles) that has failed.

Control Group
Individuals in a study who serve as a standard for comparison with the experimental group.

Coronary Arteries
The arteries that deliver blood to the heart muscle. They arise from the beginning of the aorta and form separate arterial trees that penetrate the heart muscle.

Coronary Atherosclerosis
In its severe form, the underlying disease process in coronary heart disease (also called ischemic heart disease). Atherosclerosis affects the coronary arteries, narrowing their lumen, sometimes to the point of complete occlusion. As a result of this process, blood supply to the heart muscle is reduced (see Atherosclerosis).

Coronary Occlusion
An obstruction, generally a blood clot (thrombus), superimposed on an atherosclerotic plaque in a coronary artery. It results in impaired flow of blood to some part of the heart muscle. This part of the heart muscle then dies because of lack of blood supply. Sometimes called a coronary heart attack, or simply a heart attack.

Coronary Thrombosis
The usual cause of coronary occlusion. A clot (thrombus) is formed in an atherosclerotic coronary artery, causing death of the heart muscle that the vessel supplies (see Coronary Occlusion).

Diabetes Mellitus
A metabolic disorder characterized by abnormally high levels of glucose (sugar) in the blood, generally associated with other evidences of impaired ability to metabolize carbohydrates and other nutrients properly.

Digitalis
A drug prepared from the leaves of the foxglove plant. It strengthens the force of contraction of the heart muscle, slows the rate of contraction of the heart, improves the efficiency of the heart, and promotes the elimination of excess fluid from body tissues.

Direct Costs
Expenditures for hospital and nursing home care, physicians' and other medical professional services, drugs, research, and other nonpersonal medical services.

Diuretic
A medication that promotes the elimination of excess fluid (sodium and water) from the body by increasing the excretion of urine. Several diuretic agents are now in common use.

Edema
Accumulation of excess fluid in the tissues of the body, e.g., lungs, lower extremities, and abdomen.

Electrocardiogram
A graphic record of the electric currents produced by the beating heart. The usual abbreviations are ECG or EKG.

Embolism
Occlusion of a blood vessel by a particle, generally a clot, that arises elsewhere in the circulation and is transported by the bloodstream to the site of occlusion.

Embolus
The particle that is conveyed by the bloodstream from its site of origin to a site elsewhere in the circulation where it causes obstruction (see Thrombus).

Epidemiology
The science dealing with the factors that determine the frequency and distribution of a disease in a community (population).

Essential Hypertension
A synonym for high blood pressure of uncertain cause. This is the common form of high blood pressure and is not caused by kidney or other evident disease.

Etiology
The cause, or causes, of a disease.

Fatty Streak
An anatomical abnormality in the arterial wall resulting from the accumulation of cells filled with fat, particularly cholesterol. The accumulation is located in the inner lining of the artery and causes little or no protrusion or obstruction. Although it is probably the earliest manifestation of atherosclerosis, its relationship to the subsequent evolution of atherosclerosis is not fully clear.

Fibrillation
Uncoordinated, ineffective contractions of heart muscle. Either the atria (atrial fibrillation) or ventricles (ventricular fibrillation) may be involved. Although both may be serious disturbances in rhythm because

of the irregular and rapid heart action, ventricular fibrillation is automatically life-threatening, since the chaotic action of the ventricles renders the heart totally ineffective as a pump.

Fibrin
An elastic protein which forms the essential portion of a blood clot.

Fibrinolytic
Having the ability to dissolve a blood clot.

Gangrene
Death of tissues in an area of the body, as a result of loss of blood supply.

Genetics
The study of biological heredity.

Glucose Tolerance Test
A laboratory test used in establishing the diagnosis of diabetes mellitus. Sugar, in the form of glucose, is administered by mouth or intravenously. Periodically thereafter, the urine and blood are examined for the quantity of sugar that is present. The observed levels are compared with control values.

Hemiplegia
Paralysis of one side of the body, caused by damage to the opposite side of the brain. The paralyzed arm and leg are opposite to the side of the brain damage because the nerves cross in the brain, and one side of the brain controls the opposite side of the body. Such paralysis is usually caused by a blood clot in an atherosclerotic artery or hemorrhage in an artery in the brain (see Stroke).

Hemodynamics
The study of the flow of blood and the forces involved.

Hemorrhage
Loss of blood from a blood vessel. In external hemorrhage blood escapes from the body. In internal hemorrhage blood passes into the tissues surrounding the ruptured blood vessel.

Hypercholesterolemia
An excess of the fatty substance cholesterol in the blood plasma (see Cholesterol).

Hyperlipidemia
An excess of fats (lipids) in the blood.

Hyperlipoproteinemia
An excess in the concentration of particular lipoprotein particles in the plasma (see Lipoprotein).

Hypertension
The medical synonym for high blood pressure. An increase in blood pressure above the normal range. Hypertension predisposes to atherosclerosis and may cause the overburdened left ventricle to fail. Stroke and serious kidney damage may also ensue.

Hypertrophy, Cardiac
Enlargement of the heart due to thickening of its walls because of a continuing excessive work load imposed by high blood pressure, an increased cardiac output, or disease of the heart valves or heart muscle per se.

Incidence
The number of new cases of a disease developing in a given population during a specified period of time, such as a year.

Indirect Costs
The annual productivity loss due to illness and the loss of expected lifetime productivity (discounted to the present) of those persons dying of a given disease in that year.

Infarct
An area of an organ, such as the heart, which dies as a result of an inadequate blood supply. A "myocardial infarct" refers to an area of heart muscle that has been killed because of an insufficient flow of blood, usually resulting from occlusion of one or more coronary arteries that normally supply it.

Interventricular Septum
The partition between the right and the left ventricles of the heart. Sometimes called "ventricular septum."

Intima
The inner lining layer of a blood vessel.

In Vitro
Studied outside of the living body under laboratory conditions.

In Vivo
Studied in the living organism.

Ischemia
A local deficiency of blood in some part of the body, often caused by an atherosclerotic constriction or an obstruction in the artery supplying that part.

Ischemic Heart Disease
Synonym for Coronary Heart Disease (see also Coronary Atherosclerosis, Coronary Occlusion).

Isotope
Any of two or more forms of the same element differing in atomic weight. Some are radioactive.

Lesion
An abnormality in a tissue or part of the body. Usually refers to an abnormality in structure but occasionally in function.

Lipid
Fatty substances soluble in organic solvents but poorly, or not at all, in water.

Lipoprotein
A complex of lipid and protein molecules that serves mainly to transport lipids (primarily cholesterol and triglycerides) from one organ to another. Lipoproteins are classified according to their density as high (HDL), low (LDL), or very low (VLDL). They serve not only to solubilize lipids that are otherwise insoluble in water but also to direct each particular type of lipid to particular body sites.

Lumen
The passageway of a tubular structure or organ. The vascular lumen is the passage through which blood flows inside of a blood vessel.

Metabolism
A general term to designate all chemical changes which occur to substances within the body.

Monounsaturated Fat
A fat so constituted chemically that it is capable of combining with additional hydrogen but not as much hydrogen as a polyunsaturated fat. These fats in the diet have little effect on the amount of cholesterol in the blood. Olive oil is rich in monounsaturated fat (see Polyunsaturated Fat, Saturated Fat).

Morbidity
Illness, fatal or nonfatal. A measure of the number of cases of disease. Distinction has to be made between:
1. incidence, the number of new cases of a disease developing in a given population during a specified period of time, such as a year.
2. prevalence, the number of cases of a given disease existing in a given population at a specified moment of time.

Morbidity Rate
The number of persons with a disease in relation to the total number in a given population, at a point in time (prevalence rate) or during a specified period of time, such as a year (incidence rate).

Morbidity Ratio
A ratio of the observed number of cases of disease in a population compared to the number of cases expected for that population.

Mortality Rate
The number of deaths from a specific cause in a unit of population in a specified period of time, such as a year.

Mortality Ratio
A ratio of the observed number of deaths in a population compared to the number of deaths expected for that population.

Myocardial Infarction
Death of an area of the heart muscle (myocardium) resulting from deprivation of that area of its blood supply. Usually secondary to severe atherosclerosis and occlusion of a major coronary artery.

Myocardium
The muscular wall of the heart. It is situated between the inner layer (endocardium) and the outer layer (epicardium).

Nitroglycerin
A drug (one of the nitrates) which relaxes the muscle walls or blood vessels, thereby widening the vascular channels (vasodilation). Often used to relieve attacks of angina pectoris and spasm of coronary arteries. As a result of arterial dilation, blood pressure tends to decrease.

Noninvasive Diagnostic Technique
Methods for diagnosing disease which do not require the introduction of an instrument or other device into the body.

Open Population
A study population composed of free-living individuals as opposed to institutionalized individuals (see Closed Population).

Papillary Muscles
Small bundles of muscles in the wall of the lower chambers of the heart to which the cords leading to the leaflets of the valves (chordae tendineae) are attached. When the valves are closed, these muscles contract and tighten the cords, which hold the valves firmly shut.

Paraplegia
Loss of motion in the legs and lower part of the body. This most commonly is due to damage to the spinal cord, but sometimes results from a clot or hemorrhage in an atherosclerotic artery conducting blood to the spinal cord.

Pathogenesis
The chain of events leading to the development of disease.

Pathology
The study of the nature of disease and the structural and functional changes it causes.

Placebo
A preparation containing something that can neither help nor harm the person who takes it. In testing new drugs, the experimental group is given the drug and a control group may be given a placebo that looks and tastes the same.

Plaque, Atherosclerotic
The distinctive lesion of atherosclerosis. It consists of arterial smooth muscle cells that have proliferated and migrated from the middle to the inner layer of the arterial wall, fat (particularly cholesterol), connective tissue, and sometimes calcium and hemorrhage. The result is an accumulation of tissue protruding into the lumen of the artery.

Plethysmography
Recording of the changes in the size of an organ or limb as modified by the circulation of the blood in it.

Polyunsaturated Fat
A fat so constituted chemically that it is capable of combining with additional hydrogen. These fats are usually common in liquid oils of vegetable origin, such as corn oil or safflower oil. Increase in the polyunsaturated fat content of the diet has a modest tendency to lower the amount of cholesterol in the blood (see Monounsaturated and Saturated Fat).

Prevalence
The number of cases of a given disease existing in a given population at a specified point in time.

Primary Hypertension
A synonym for essential hypertension and commonly known as high blood pressure. The high blood pressure is not caused by kidney or other evident disease.

Primary Prevention
Measures taken so that a given disease does not occur.

Prosthetic Blood Vessel
An artificial substitute for part or all of a given blood vessel.

Pulmonary Artery
The large artery which leads from the right ventricle of the heart to the lungs. It carries venous blood to the lungs for oxygenation. This is the only artery in the body that carries unoxygenated blood.

Pulmonary Circulation
The blood vessels of the lungs. From the right ventricle, blood is brought to the lungs by the pulmonary artery and returned from the lungs to the left atrium and ventricle by the pulmonary veins.

Radiograph
A synonym for an x-ray photograph of a part of the body.

Rehabilitation
The return of a person disabled by accident or disease to the maximum attainable physical, mental, emotional, social, and economic usefulness, and, if employable, an opportunity for gainful employment.

Risk Factor
An epidemiologic concept that refers to an attribute of an individual, a human population or their environment that increases the likelihood of developing disease, e.g., the complications of atherosclerosis, such as coronary heart disease, stroke, and peripheral arterial disease. The concept implies that the presence, magnitude, and duration of one or more risk factors for the atherosclerotic diseases in an individual increases the prospects that the individual will develop atherosclerosis and its complications; a reasonable corollary is that reduction or removal of the risk factors will diminish the likelihood that the individual will develop the complications of atherosclerosis. Best established as risk factors for the atherosclerotic diseases are: hypertension, hypercholesterolemia, and cigarette smoking.

Saturated Fat
A fat so constituted chemically that it is not capable of combining with any more hydrogen. These are usually the solid fats in milk, butter, meat, hydrogenated vegetable fats, etc. A few vegetable oils, e.g., coconut oil and palm oil, are high in saturated fats. A diet high in saturated fat tends to increase the amount of cholesterol in the blood.

Secondary Prevention
Measures taken to prevent recurrence of disease.

Serum
The fluid portion of blood that remains after the cellular elements have been removed by coagulation. It is different from plasma, which is the cell-free liquid of uncoagulated blood.

Shock
The condition of collapse of the circulatory system. The signs of shock include weakness, extreme pallor, cold and moist skin, weak and rapid pulse, irregular and shallow breathing, thirst, nausea, scanty secretion of urine, and low blood pressure.

Sodium
A mineral essential to life, found in nearly all plant and animal tissue. Table salt (sodium chloride) is nearly half sodium. In some types of heart disease the body retains an excess of sodium and water, and therefore, treatment includes restriction of sodium intake. High sodium intake has been implicated as one factor in the causation of high blood pressure (hypertension).

Stroke
Stroke is a term designating the acute occurrence of symptoms and signs of loss of neural function caused by disease of the arteries or veins serving the central nervous system. It results in a loss of brain function due to infarction or hemorrhage. Focal ischemia or infarction is usually the result of occlusion, while hemorrhage is the result of rupture of a blood vessel.

Syndrome
A set of symptoms that occur together and are therefore given a name to indicate that particular combination.

Systemic Circulation
The circulation of the blood through all parts of the body except the lungs, the flow being from the left lower chamber of the heart (left ventricle) through the body, back to the right upper chamber of the heart (right atrium) (see Pulmonary Circulation).

Transient Ischemic Attack (TIA)
TIA is a clinical entity characterized by sudden loss of neural function with full restitution usually within 1 but always within 24 hours. It is not accompanied by gross anatomical or pathological change in the affected neurons. Atherosclerosis is only one of the many causes for TIA. For example, high or low blood pressure, abnormalities in the blood constituents or microemboli from the cardiac valves or chambers, as well as cardiac dysrhythmia, alone or in association with atherosclerosis, can cause TIA's.

Thrombolytic Agents
Substances that dissolve blood clots.

Thrombosis
The formation or presence of a blood clot (thrombus) inside a blood vessel or cavity of the heart.

Thrombus
A blood clot that forms inside a blood vessel or cavity of the heart (see Embolus).

Unsaturated Fat
A term for both monounsaturated and polyunsaturated fats.

Urography
Radiographic visualization of the urinary tract after injecting contrast material.

Vasospasm
A constriction of the lumen of the vessel by contraction of its muscular wall. It may produce angina at rest or during exertion, particularly in vessels partially occluded by atherosclerotic disease.

Vein
Blood vessels that return blood either to the right side of the heart or to the left side of the heart. Systemic veins return blood to the right side of the heart from all tissues and organs of the body except the lungs; the right ventricle then delivers the venous blood to the lungs for oxygenation. Pulmonary veins return oxygenated blood from the lungs to the left side of the heart for distribution by the left ventricle, by way of the arterial tree, to all organs and tissues of the body.

Ventricle
The heart consists of two muscular pumps (ventricles) each of which is supplied by a chamber (atrium). The left ventricle pumps oxygenated blood by way of the systemic arteries throughout the body. The right ventricle pumps unoxygenated blood by way of the pulmonary artery to the lung.

Vertigo
A sensation that the external world is revolving around the patient.

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